Development of Microelectronic based biosensors

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Abstract

Biosensors offer the opportunity to sense the biological world providing valuable information for medical diagnostics, analytical chemistry, environmental monitoring and fundamental research. Convergence of engineered (bio)chemical surfaces with micro- and nano- systems promises tremendous advances and potential cost reductions in biotechnology. This paper introduces some key challenges facing biosensor development, focussing on opportunities that arise from microsystem platforms utilising novel materials and processes. Examples from our work are presented illustrating the implementation of acoustic wave sensors and novel FET-type sensors.

Introduction

Biosensors based on microsystems (utilising microelecronic fabrication technologies) are of great interest, with the main driving force for their development based upon their simplicity in function as well as their small size, faster response and the opportunity for lower costs. The particularities of the microelectronic technologies like miniaturisation, mass (batch) fabrication which enables standardisation and cost reduction, arrays (parallelism), as well as system integration are exploited in all the fields involved in biosensor development. With the increasing number of fabrication methods available, the diversity of the materials is continuously expanding.

A biosensor integrates a physico-chemical transducer in direct contact with a biological recognition element sensitive to the analyte of interest. For instance, antibodies are used as biological probes to measure antigen concentrations in blood, but can also be manipulated to allow for the measurement of toxic substances present in the environment. DNA probes immobilised at sensor surfaces recognise their complement, and, formatted in arrays, allow DNA-fingerprinting or genotyping to track hereditary diseases. Cells can be cultivated on top of solid-state transducers and used in pharmaceutical research for high throughput drug screening and toxicity studies. More advanced applications, are addressing the specific integration of neurons with electrical semiconductor devices, creating new opportunities for the development of neuro-sensors, bionic systems and eventually neuron-computers. In general, biosensors are expected to change the way in which we obtain information about our health, the food quality and the state of the environment.

While current state-of-the-art research is focussed towards the development of highly sensitive and innovative sensor configurations utilising these new materials and processes, there is growing attention being directed at realising more "functional and user-friendly" biosensors that facilitate rapid and easy-assay investigations. Such systems greatly enhance their operational usage in the wider community and hence provide a greater access (and acceptance) of the underlying novel technology. To address these issues, we are focussing our efforts towards the development of a *Biosensor-System-In-a-Package* (BioSIP) concept, whereby unique packaging solutions are investigated that aim to integrate the microfluidics, transducer and (bio)chemical interface components. These packaged biosensor modules will offer greater user flexibility, high sensitivity and stability through the incorporation of novel transducers configurations, organic chemistry surface chemistry and optimised (specificity, coverage, density, orientation,...) biochemical probes.

This paper introduces some of the key issues facing biosensor development, focussing on the opportunities that arise from microsystem platforms utilising novel materials and processes, addressing key enabling technologies (surface chemistry, transducers and packaging). Several examples are presented to illustrate the inter-disciplinary nature of this activity, including acoustic wave sensors and novel FET-type sensors utilising non standard materials, like conjugated polymers and GaAs.

Surface chemistry for biosensors

A common bottleneck in the development of biosensors is the insufficient stability and reproducibility of the biological interface, *i.e.* the interface between the inorganic transducer surface and the biological affinity elements, in the different environments of their applications. In addition, the increasing miniaturisation of biosensor transducers (and thus of their active areas) and the need for a higher sensitivity impose more severe demands upon the process of coupling biomolecules to transducer surfaces. Therefore, controlled thin film structures should be realised in which the bio-

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affinity elements may be arranged and addressed in reproducible and controlled geometric surroundings. One of the most promising methodologies in order to achieve this, is the use of Self-Assembled Monolayers (SAMs). Since the transducer surfaces of the affinity-based biosensors (*e.g.* immunosensors) developed at IMEC are composed of metals and/or oxide materials, our surface chemistry research is focussing on the covalent attachment of antibodies on metal (ie, Au) and on oxide surfaces (ie, SiO_2 and Ta_2O_5) (Fig. 1).

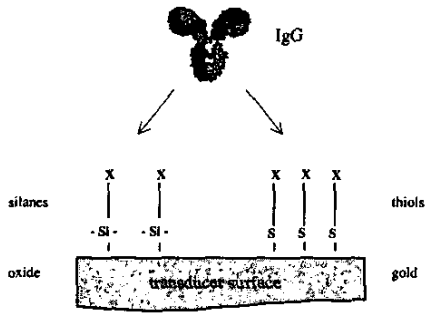

Fig. 1: Methodology for (bio)chemical modification of microelctronic transducer surfaces.

Our approach to realise bio-reactive Au surfaces is based on the deposition of mixed SAMs of thiol compounds on clean Au (Fig. 2) [1,2]. One type of thiol in the mixed SAM carries a functional group able to attach the receptor molecules, *i.e.* the antibodies. The other thiol compound allows to minimise the non-specific adsorption of undesired bio-species and thus it contributes to a solely specific interaction of the analyte with the immobilised antibodies.

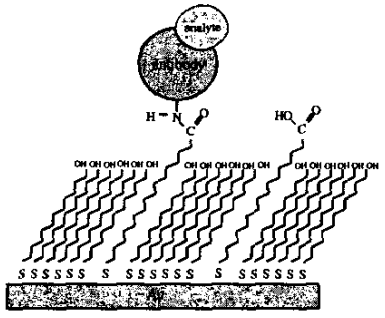

Fig. 2: Schematic presentation of a mixed Self-Assembled Monolayer (SAM) of thiols which presents two functional groups: one to allow the attachment of antibodies (i.e. COOH functionality) and the other one to minimize non-specific adsorption (i.e. OH functionality).

For the functionalisation of oxide surfaces, the use of silane compounds has been evaluated [3,4]. However, the formation of SAMs from silane molecules is only possible when they are produced under the proper experimental conditions. In addition, bio-reactive functional groups have to be created *in situ* after SAM deposition. Therefore, the methodology applied to enable the realisation of bio-reactive silane SAMs on oxide materials consists of the deposition of non-polar precursor chlorosilanes on the oxide surface, followed by the performance of surface reactions in order to introduce bio-reactive functional groups, *e.g.* COOH or NH_2 groups (Fig. 3). The main focus in the evaluation and optimisation of this methodology was the effective formation of SAMs from chlorosilanes and the introduction of functional groups on the resulting chlorosilane SAMs [3,4].

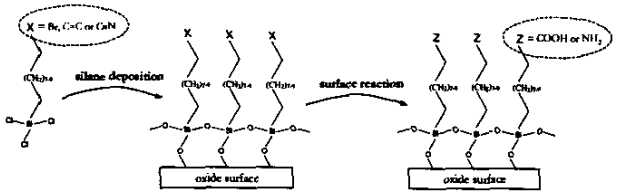

Fig. 3: Schematic presentation of the methodology for the realisation of bio-reactive silane SAMs on oxide surfaces in two steps. Left: the deposition of a precursor silane SAM; right: the performance of a surface reaction for the introduction of functional, e.g. COOH or NH_2, groups.

For the realisation of affinity-based biosensors, e.g. immunosensors, different types of antibodies, i.e. conventional antibodies, chemically modified conventional antibodies and recombinant camel antibodies, are coupled onto the SAM-coated surfaces. Depending on the type of surface and on the type of antibody, these receptors are immobilised onto the surface covalently or via adsorption and in an oriented or random fashion. In order to detect a specific analyte, by means of antibody receptors, direct or indirect assays can be developed. In a direct assay, the binding event of the analyte with its corresponding immobilised receptor generates a direct response on the transducer level. As a consequence, this is the assay of choice to enable the realisation of low-cost, fast and simple biosensors. When the sensitivity and/or selectivity of the direct assay are inadequate, indirect assays are developed. This kind of assay is a more complex way to detect a bio-analyte and consists of various, subsequent binding events, resulting in a higher sensor response.

Microsystems for biosensors: materials & technology

A large variety of solid-state devices can be used as transducers for a biochemical interaction which generates a change in mass, temperature, electrical potential etc. Amongst these, silicon semiconductor devices have been the first to emerge and their potential for electrochemical sensing applications has been demonstrated and extensively investigated [5].

New materials have been proved to have attractive properties for sensor applications. For instance, the interesting electronic properties of GaAs has started to be exploited in the area of sensors since they promise a larger sensitivity compared to that of silicon devices. GaAs-based heterostructures provide attractive electronic properties [6]

for the implementation of potentiometric sensing devices. GaAs field-effect devices have been used to stimulate/detect the electrical activity of single biological cells like neurons and cardiomiocytes [7].

During recent years, polymeric materials have gained a wide theoretical interest and practical applications in sensors. The features that make polymers attractive for these applications are their relative low-cost, the physical compatibility with IC and interconnected techniques and the biocompatibility of many of these materials. The discovery of semiconducting conjugated polymers and the ability to dope these polymers over the full range from insulator to metal has resulted in the creation of a class of new materials that combines the electronic and optical properties of semiconductors and metals with the attractive mechanical properties and processing advantages of polymers [8]. Field-effect transistors using an organic semiconductor as an active layer material have received considerable attention and their performances are constantly improving [9]. Such transistors may eventually replace their silicon counterparts in applications where single-use devices are desirable. The ability of an enzyme-modified organic-based thin-film transistor to detect glucose has been recently demonstrated [10]. The detection principle is based on the electric-field enhanced conductivity that occurs in organic semiconductors similar to the crystalline ones.

Piezoelectric materials like quartz, lithium niobate etc can be exploited as well as a biosensor transducer due to their ability to generate and transmit acoustic waves in a frequency-dependent manner [11]. A particular type of Acoustic Wave (AW) device of significant potential is the Love wave mode device [12]. Love wave mode devices are characterised by acoustic waves that propagate in a layered structure consisting of a piezoelectric substrate and a guiding layer, usually a low stress thick oxide [12]. They have a pure shear polarisation with the particle displacements being parallel to the surface plane. A Love wave can only exist if the shear velocity in the layer is less than the shear velocity in the substrate [13]. This results in slowing down the acoustic wave in the substrate, thus confining the acoustic wave energy to the surface layer. The mass sensitivity of the device is mainly determined by the thickness of the guiding layer (normalised to the acoustic wavelength). For increasing layer thickness, wave guiding becomes more efficient, causing the mass sensitivity to increase, but at the cost of increasing the attenuation of the acoustic signal.

Beside the transducer and signal conditioning circuit fabrication, micropatterning of biological substances like proteins and DNA on surfaces can be also achieved using lithographic techniques initially developed for the semiconductor industry [14]. The realisation of miniaturised total analysis systems [15] with micron-size fluidic channels fabricated in silicon, glass and plastic materials has enabled the reduction of both the sample size and the detection time of biosensors.

From a technological point of view, the integration of all the system components remains the most challenging part. The components are most frequently fabricated using different materials and technologies and the most important requirement is to create compatible interfaces. The reduced cost and cross contamination can be addressed via the disposability issue. The general system architecture has to be a modular one – the parts being in contact with the biological samples need to be separated from the transducer and/or read out electronics. Packaging solutions for biosensing applications have to provide more than just environmental protection, but electrical connections, mechanical support as well as biocompatibility.

Packaging of Biosensors

One significant challenge concerns the packaging of microelectronic-based biosensors. Successful packaging solutions for devices contributes significantly to the overall functionality and cost effectiveness of a disposable sensor subsystem, which is highly desired for the medical diagnostics market, for example. Packaging of such devices is still at a very early stage in development and usually, the packaging for a product is highly application specific. One major issue concerns the connection of fluidic, mechanical and electrical (and possibly optical) systems from the macroscale to the microscale. Further to this, biocompatibility constraints also influence the selection of existing materials and drive the development of new materials. Microelectronics based packaging technologies can be adapted to address these issues. Standard IC packaging techniques are used for the integration of fluidic structures with transducers, utilising conventional flip-chip bonding techniques (ie, high temperature, force) and non-convential "polymer gluing" techniques (ie., photo-patternable polymer, SU-8). These modules are then flip-chip mounted on disposable "card like" carrier with the fluidic, electrical (or optical) interfaces being respected. Moreover, flip-chip offers the highest speed electrical performance of any assembly method. Eliminating bond wires reduces the delaying inductance and capacitance of the connection and results in high speed off-chip interconnection.

Fig. 4 illustrates the flip-chip bonding technique of microsystem components and Fig. 5 shows an application of the technique for the AW based biosensor (left) and for a FET-type sensor (right). Here, for example, the AW device, together with its dedicated microfluidic chip, is mounted on a ceramic carrier and connected electrically using solder or conductive adhesive bumps. The mechanical stability of the structure is aided by a polymer underfil material.

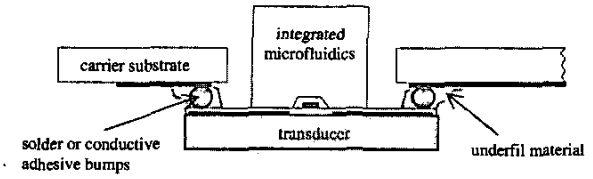

Fig. 4: Flip-chip bonding technique for Microsystems based biosensors.

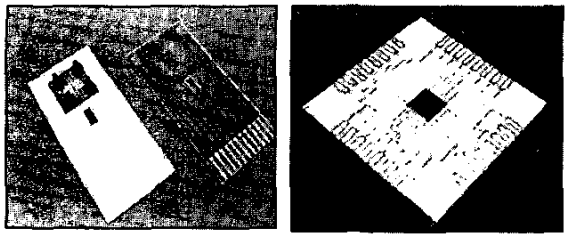

Fig. 5: Example of an AW sensor (left) and a FET-type transducer (right) mounted on ceramic carriers.

Apart from the obvious requirements like simple fabrication, self-life and cost aspects, materials for miniaturized biosystems must be also compatible with the biological environment. Creating biomimetic surfaces with regions with high affinity towards the analyte species and repellent regions in order to reduce undesired protein adhesion will improve the sensor performances and viability.

Examples of biosensors

Acoustic Wave devices for biosensors

AW devices are proposed as an alternative system, to that of existing optical techniques, for the direct detection of low analyte concentrations of biological species in solution. AW devices can measure minute mass changes on a small (mm^2) sensing area defined by a flow cell. The mass increase due to the adsorption of the biological material leads to an acoustic velocity decrease, which can either be monitored in an open loop configuration by a network analyser, or in a closed loop configuration by an electronic oscillator. In both cases the acoustic wave probing the surface is generated at a frequency in the 100 MHz range by a set of interdigitated transducers (IDT) patterned on the piezoelectric substrate (Fig. 6). While AW devices are expected to reach 'high sensitivities comparable to current result obtained with optical methods (fluorescence, surface plasmon resonance), the lack of optical components and moving parts makes this technology attractive in terms of compactness, low power consumption and robustness. The technology is very close to that used for making quartz resonators and high-frequency SAW filters in the electronics industry so reliably obtaining large production quantities has been proven to be feasible.

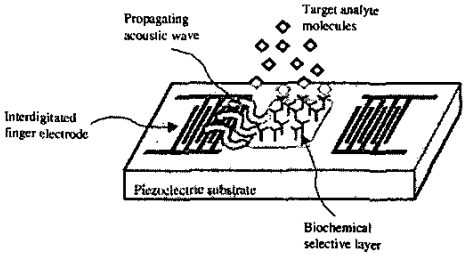

Fig. 6: General structure of an AW sensor.

We have fabricated AW devices on 500 μm thick ST-cut quartz wafers, on which 200nm thick sputtered Al interdigitated electrodes are patterned. Subsequently, the surface is coated with a 1.13μm PECVD silicon dioxide layer acting as the guiding layer, and at last the 4.9 x 5.4 mm^2 sensing area is coated with 10nm Ti and 50nm Au. The phase of the AW delay line is monitored at a fixed frequency using a network analyser (HP4396A) at 123.200 MHz (Fig. 7). The phase shift is converted into a frequency shift due to the linear phase to frequency relationship recorded in the Bode plot. The observed phase shift leads to a frequency shift (as would be observed in a phase locked loop configuration) which in turn is converted into an absorbed mass change through the sensitivity of the device.

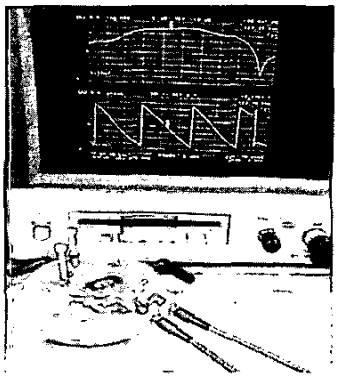

Fig. 7: Measurement configuration for the AW sensor.

Experiments were performed to demonstrate the potential of the AW based biosensors for the detection of cancer markers, as an application of disease screening in a clinical environment. Identification of certain tumour targets, so-called "tumour antigens" opens the door to new approaches in cancer treatment and control of cancer therapy. Prostate cancer, for instance, is the second leading cause of cancer deaths in men in many industrialised countries. Tests have been developed to detect prostate cancer at an early stage and in these retrospective studies, Prostate Specific Antigen (PSA) has been shown to advance the diagnosis of prostate cancer.

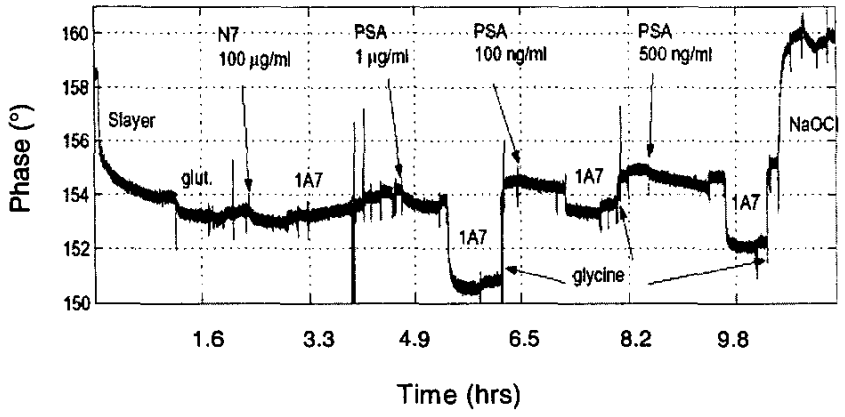

Fig. 8: AW sensor response to different PSA concentrations using direct and indirect techniques.

Fig.8 shows the AW sensor response to different PSA concentrations using both direct and indirect sensing techniques. A self-assembled monolayer of S-layer proteins [16] is formed on top of the gold substrate of the AW device. After cross-linking this monolayer with glutaraldehyde, a specially engineered camel antibody against PSA is covalently attached on top of the biological recognition layer. This recombinant antibody consists only of the VHH region of a camel antibody. It has a small molecular weight (15 000 Da) that results in a high specific coverage of the sensor surface. Once our biological recognition element is coupled to the surface, we develop a direct or indirect assay to detect the specific analyte.

The sensor response of the direct binding of PSA is in the range of the noise level of the AW transducer. In the indirect binding a conventional antibody is introduced and recognizes the bound PSA on the surface. This binding event generates much larger sensor responses because the molecular weight of a conventional antibody (150 000 Da) is 5 times bigger then the molecular weight of the PSA (30 000 Da). It is clear that in this specific example of an indirect assay, the sensitivity of the PSA detection has increased significantly compared to the direct detection of PSA. In between the different concentrations the PSA conventional antibody complex is removed from the surface by the injection of a 10mM glycine buffer with pH2.2. At the end of the experiment the S-layer is removed from the gold substrate of the AW by the usage of NaOCl.

Polymer-based Ion-Sensitive Field-Effect Transistors (PolymerISFETs)

Within the main goal of developing low-cost (disposable) transducers for bioanalytical applications, we have realised a polymer-based field-effect transistor able to detect both charged and uncharged chemical species in aqueous media. Although the concept of ion-sensitive field-effect transistor (ISFET) [17] has been proposed more than 30 years ago, only very few practical applications have emerged until now. Conventional ISFET sensors are manufactured by CMOS technology on silicon substrates and the long-term stability problems correlated with the fabrication and packaging costs are major limiting factors for the practical applications. On the other hand, for health-related applications single use microsensors are highly desirable due to the safety requirements and limited lifetime of the biological components involved. For such applications, organic semiconductor materials present several advantages such as simpler fabrication techniques compared to silicon, compatibility with plastic substrates and biocompatibility. We have realised a prototype in which the polymer poly(3-hexylthiophene) regioregular (P3HT) is used as the semiconductor layer (Fig. 9). The chemical sensitivity of these organic detectors has been demonstrated for protons and glucose [10]. Evaporated Ta_2O_5 is used as H^+-sensitive gate insulator. A reference electrode is used to ensure a stable electrical contact with the solution phase and it plays the role of the gate in a conventional transistor structure. The pH-dependent potential occurring at the solution/insulator interface modifies the density of the accumulated charge in the organic semiconductor at the interface with the dielectric and, consequently, the current in the transistor. Using the same pH transducer, a glucose-biosensor can be realised simply by anchoring an enzymatic layer (glucose oxidase) onto the gate insulator [18]. The hydrolysis of the glucose, catalyzed by the enzyme, increases the proton concentration at the Ta_2O_5 surface and, consequently, generates a current variation proportional to the glucose concentration (Fig. 9). Sensitivity and selectivity towards different ions or neutral molecules and biomolecules can be achieved by adding specific recognition layers onto the gate insulator.

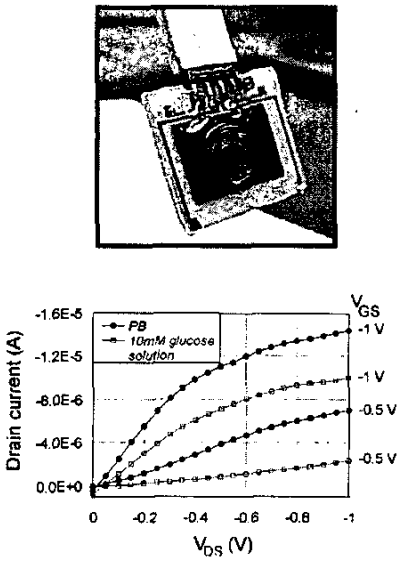

Fig. 9: Photograph of the device encapsulated with silicon rubber (top) and glucose response (bottom). The current decreases when the glucose is present in the buffer solution (local pH decreases) [18].

GaAs potential for chemical sensors and biosensors

The electro-optical performance of the semiconductor devices is critically determined by the electronic properties of the semiconductor surface, especially the band bending at the semiconductor surface and the surface recombination velocity [19]. These properties in turn depend on the density of states and the energetic distribution of the surface states. The surface properties can be in principle influenced by the organic layers, able to selectively bind biological species, adsorbed onto the semiconductor surface.

In pursuit of a labelling-free affinity transduction principle, hybrid organic/inorganic III-V technology is currently the subject of intense research [20,21]. The III-V field-effect transistors (FETs) usually have a much higher transconductance than their silicon counterparts. The exact values depend on gate length, thickness of the channel layer, doping and mobility, but for GaAs-MESFETs transconductance values in the range of 200-300 mS/mm and, respectively, 600-700 mS/mm in the case of HEMTs, HFETs or MODFETs are pretty common (expressed per unit gate width) [22]. This fact is due to the inherently higher mobility of electrons in GaAs (6 to 7 times higher than in silicon for normal doping levels). The high transconductance bestows on III-V transducers the potential of very high sensitivity. Exact control over the growth of III-V semiconductors via molecular beam epitaxial technique, as opposed to silicon FETs, which are produced by implanting dopants to create a channel layer, allows for the exact control over the (opto-)electronic properties of the substrate/device, which can further enhance the sensitivity of the transducer.

The development of the sensor technology based on III-V semiconductors is dependent on the ability to prepare stable semiconductor surfaces with tailored surface properties. The surface chemistry, which is very versatile on III-V materials, can have a beneficial impact on the (biological) sensor sensitivity [23]. Thiols, dicarboxylic acids, phosphonates, silanes, inorganic sulfides etc. can be anchored onto GaAs semiconductors. The absence of a stable native oxide is an advantage since it allows for a direct contact between the organic layer and the semiconductor crystal. In this way direct access to the surface states is possible, which enables the tuning of the electronic properties and opens other ways of sensing than the classical field-effect over a distance.

Part of our current research activity is dedicated to the development of a hybrid organic/inorganic III-V semiconductor technology for affinity biosensor applications. In such a biosensor system, the transducer is basically a modified MESFET. The conductance of the channel between the two electrodes is changed by adsorbate-induced perturbation of the surface potential. Simply put, the transducer behaves as a non-biased field effect transistor (FET) wherein the metallised gate has been replaced by a molecular gate. In a proof-of-principle experiment, the molecular gate is formed by two organic self-assembled monolayers, sodium 2-mercaptoethanesulfonate (MES) and 1-methyl-4-{(E)-[4-(dimethylamino)phenyl]diazenyl} pyridinium iodide (AzPy+) respectively, deposited in consecutive steps (Fig. 10, top). To assess the influence of the organic monolayers on the electronic properties of the gateless MESFET, we have measured the I-V curve of this organic/inorganic hybrid after each assembly step.

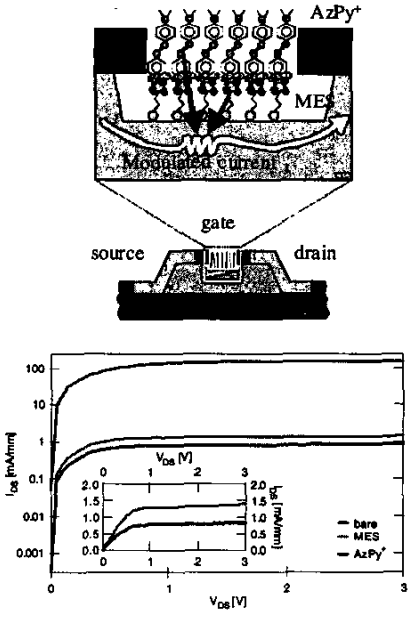

Fig. 10: Schematic representation of a gateless MESFET with organic monolayers self-assembled on the gate area (top) and typical I-V curves recorded from hybrid organic/inorganic MESFETs (bottom).

Using a parameter analyser, a voltage signal (VDS), applied between the source and drain contacts of various hybrid MESFETs with different geometry, was swept between 0 V and 3 V, and the resulting current between source and drain (IDS) was recorded. Fig. 10 (bottom) shows two typical I-V curves. The current is expressed in [mA/mm gate width] in order to compensate for differences in gate widths between the measured MESFETs. The I-V curves show the current before MES deposition (marked "bare"), after the self-assembly of MES (marked "MES") and after the cationic exchange of AzPy+ (marked "AzPy+"). The current is depicted on a logarithmic scale, while on the insert showing only the MES and AzPy+ current, the scale is linear.

The observed response is generated by the modulation of the electronic properties of the semiconductor due to the frontier orbital interaction between the surface states of the semiconductor and the molecular adsorbates [23,24]. In this case, the interaction leads to a current decrease by re-distribution of the charge carriers trapped in the surface states. Consequently, the space-charge region (SCR), which controls the current flowing in the transistor, extends further into the semiconductor (larger band bending) and determines the drain-source current drop.

Although the effect of the adsorbed species onto the electronic behaviour of the device is obvious, a more fundamental investigation of the frontier orbital mixing theory is needed to explain and fine-tune the sensitivity of these transducers in order to unlock their fullest potential. Controlled surface modification strategies still seem to be ill quantified and characterised by limited reproducibility. Recent research focuses on the relationship between the physicochemical properties of the surface structure and composition and the semiconductor electro-optical properties [23,24]. A better understanding of this enigma would facilitate customising adsorption-controlled sensor characteristics to produce desired sensitivity, selectivity, kinetics and robustness. Currently these relationships are still largely empirical and a molecular toolbox to tune sensitivity and selectivity of the hybrid semiconductor sensor has yet to be awaited. It seems that the hybrid semiconductor surface has just been scratched.

Conclusions

This paper has presented some of the enabling technologies (surface chemistry, tranducers and packaging) crucial for the successful development of microelectronic based biosensors. The integration of these key system components is a significant challenge. While components are frequently fabricated using different materials and technologies, the most important requirement is the creation of compatible interfaces. The important role of surface chemistry for the creation of (bio)chemical functional surfaces, needs to be balanced with the engineering of materials and processes, in order to realise optimal microsystem platforms for biosensor applications.

Depending on the final application, different materials and technologies can be used for the development of physico-chemical transducers. For monitoring of affinity-type biological interactions, AW based sensors show significant promise. Microfabricated AW sensors were presented that showed a sensitivity towards different PSA concentrations using both direct and indirect sensing techniques. Further optimisation of the transducer material characteristics will lead to enhanced sensitivities and operation.

Polymer based microsensors are good candidates for environmental and health-related applications where simple and low-cost detection systems are required. A polymer-based field-effect transistor has been realised for the detection of both charged and uncharged chemical species in aqueous media. Although the sensitivity of these organic detectors has been demonstrated for protons and glucose, the lack of stable solution-processable organic semiconductors with low and reproducible defect densities is the main constrain for this kind of applications.

Hybrid organic/inorganic III-V semiconductor technology for affinity biosensor applications was demonstrated via the use of a novel modified MESFET transducer. While a proof-of-principle was demonstrated showing the effect of the adsorbed species on the electronic behaviour of the device, more fundamental investigations are needed to address the specific relationship between the physicochemical properties of the surface structure/composition and the semiconductor properties of the device. This facilitates a better understanding of the sensing mechanism, leading to enhancement of the sensor sensitivity and selectivity.

Future work is focused towards improving the overall sensing functionality of the devices with the aim of exploiting prototype systems in medical applications, investigating their impact in an operational environment.

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