

Design for MOSIS Educational Program

(Research)

Project Title: Real-time Conversion of Signals from Biological Recognition Events into Electrical Signals

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Real-time Conversion of Signals from Biological Recognition Events into Electrical Signals

1. Project Description

The objective of the proposal is to develop a hybrid biomolecular system that optimizes the interface between a biological membrane and a silicon circuitry for the accomplishment of dynamic, real-time conversion of biochemical signals of the recognition events into electrical signals.

1.1 Background

The potential use of the spores of *Bacillus anthracis* (BA) as a weapon of biological terrorism has rekindled interest in the rapid methods for their detection and identification of the spores of these bacteria. Bacterial detection methods have to be rapid and very sensitive since the presence of even a single pathogenic organism in the body or food may be an infectious dose. Although substantial technological progresses have been made in biological warfare detection, portable, rapid and sensitive systems with immediate interpretation of results still do not exist. Much of the technology being used, such as chromatography, infrared or fluorescence spectroscopy, polymerase chain reaction (PCR), bioluminescence, flow cytometry, impedimetry and many others are large, expensive, or require sophisticated, relatively time-consuming, often extensive analysis procedures.

The outer face of macromolecular biological assemblies like bacteria consists of an exosporium, a coat for the dormant spores composed of proteins, sugars, glycoproteins and lipids, therefore, they carry charged or chargeable groups on their outer surface creating an electric double layer upon contact with the aqueous phase. Under the electromotive force, an equilibrium potential of the electrode or sensor vs. a suitable reference electrode can be measured by potentiometry. We have incorporated the biological recognition components such as peptides, aptamers, sugars, or antibodies in the sensing layer on the surface of an electrode, enabling the bacterial spores to be recognized by the measured potential change during the binding. This specific reaction between the biological recognition component and bacterial spores can be observed without any pre-concentration or separation process. The developed method is rapid, highly specific, and label-free monitoring of bacterial spores.

Ionic surfaces on transistors have been applied in the field of Ion Sensitive Field Effect Transistor (ISFET). The response of the ISFET system on a stepwise increase in the electrolyte concentration is a transient change of the output voltage, which is related to the surface charge density of the ISFET gate oxide. The gate has been coated for instance with an ionic membrane (with specific ligands) and the changes in ion concentration resulting from the binding of the analyte or from the analyte present due to the binding will alter the electrical potential of the membrane and thus that of the gate (as an example: BIOCHEMFET, US Patent 4,562,157).

The chemically sensitive or ion-sensitive FET (ISFET) is fabricated by forming a sensing layer on top of conductive gate electrode or by replacing conductive gate and gate oxide

by a sensing layer. The threshold voltage and drain current of an ISFET is modulated by the material properties of gate electrode in the presence of specific chemical or biological signatures. By measuring the change in drain current, chemical or biological sensing is performed. Different types of sensing layers can be deposited within the same chip to detect various chemical or biological elements. In addition, on-chip readout circuitry can be integrated monolithically to form low-cost and small form factor chemical sensors. It is also feasible to integrate chemical or biological sensors with communication circuits for portable applications or remote sensing, where readout data will be sent to a base station wirelessly for further analysis.

1.2 Previous results

A portable peptide – containing potentiometric biosensor for direct identification of bacterial *Bacillus subtilis* (*B. subtilis*) spores has been developed at Polytechnic University. The peptides for specific recognition of *Bacillus subtilis* spores were immobilized by polysiloxane monolayer immobilization technique. The sensor translated the biological recognition event into a potential change by detecting *B. subtilis* spores in a concentration range of $1 - 1.2 \times 10^7$ / 100ml. The sensor exhibited highly selective recognition properties towards *Bacillus subtilis* spores over other kinds of spores with the selectivity coefficients for other kinds of spores in the range of $0 - 1.5 \times 10^{-5}$. The biosensor system has the specificity to distinguish the *Bacillus anthracis* spores in a mixture of *Bacillus subtilis* and *Bacillus cereus* spores (2).

We have conducted research on electrically conducting polymers for over ten years and have today a technology to use inkjet printing with the electronic ink based on polyaniline [2]. Eventually we plan to use electrically conducting polymers as components in the FET so that we can build flexible wireless sensors, but in this proposed research we shall use only these polymer film coatings with patterned FET's to build the technology for the signal processing.

1.3 Proposed research plan

Our objective is to

A. study the effect of the ionic polymer film coated on FET substrate on the electrical properties of the polymer/FET structure. This work is the first step to investigate the conversion without the biologically sensitive ligands.

B. To study the effect of the ion-sensitive polymer film modified with the specific ligands on the ionic current in the polymer/FET assembly in the presence of bacterial spores.

2 Project Size, ISFET Design and Fabrication

Although there are various methods for fabricating ion-selective FETs, we would like to concentrate on standard CMOS process that is available through an external foundry such as MOSIS [3]. In a standard two metal layer AMI 1.2 μm CMOS process through MOSIS, nFET and pFETs are fabricated with a minimum channel length of 1.2 μm . However, for our application, channel length of 50 μm or higher is desirable for ease of post processing. The fabrication steps of our proposed ISFET are compatible with standard CMOS fabrication process. In ISFET the gate electrode is formed by a metal 1

(M1) aluminum interconnect that is aligned and interconnected with polysilicon gate. A window, directly above the M1 electrode, is etched through the protective glass encapsulation, and sensing material is deposited on top of the Al gate electrode. All these processing steps except the deposition of sensing layer can be performed externally through MOSIS [3,4].

Our first test chip will consist of 10-16 individually accessible FETs and ISFETs. The number of devices is limited by the number of I/O terminals on the periphery of a 2.2 mm x 2.2 mm chip. The surfaces will be spincoated with polymers which are modified with the specific ligands defined above. We shall focus in the first step on the detection of *B. subtilis* as it is harmless and we have a strong experience with it. After the initial phase of investigation, ISFETs will be fabricated in TSMC's 0.25 μm or 0.35 μm technology through MOSIS. The higher device density in these process technologies will allow us to integrate on-chip read-out, signal processing, and communications circuits to form monolithic bio/chemical sensors.

We have conducted research on electrically conducting polymers for over ten years and have today a technology to use inkjet printing with the electronic ink based on polyaniline. In this proposed research we shall use only these polymers films with FET's but not to pattern them as components of the actual FET yet.

3 Test and Characterization

There are several techniques to measure the sensitivity of ion-sensitive FET's in response to a chemical or biological signature. For example, a fixed DC voltage can be applied to the gate of ISFET and the change in drain current can be measured as a function of ion activity on the sensing material. Alternatively, one could measure the gate voltage required to keep the drain current constant. Initially, these measurements will be performed using off-chip signal generators and readout circuits. However, in future readout circuits consisting of operational amplifiers, comparators, and A/D converters will be integrated on-chip. The required measurements for characterizing ISFET's can be performed by probing the input/output pads in a probe station or after wire bonding the chip to a chip-carrier.

4 Potential Impact and Summary

The integration of biological sensing with electronic signaling with our approach builds a strong basis for developing the concept of Biology on Silicon. Our initial approach is based on 1. the obtained expertise in specific ionic interactions between specific ligands and bacteria, 2. our understanding of organic ion-sensitive electrical conductors; electrically conducting polymers and 3. on a expertise of silicon based circuits and field effect transistors. The potentiality in our success is extremely great, and with this success we can expand our project with bilayer membranes with ion channels for amplification, to artificial cell analogues and eventually to biological cells on silicon.

The immediate impact on educational is the development of Biosensors Course. We shall be able to develop a novel content in the course with strong emphasis on experimental research-based learning. In addition, students will have the opportunity to work with state of the art CAD tools to design integrated sensors and signal processing circuits.

3.6. REFERENCES

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