Microsensors Arrays Manufacture Using the NanoeNabler™
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Abstract – Novel method for microarrays manufacture using BioForce NanoeNabler™ was successfully employed for developing sensors for biomedical applications, namely pH and glucose monitoring. It is envisaged that findings of this work would form the basis for miniaturised diagnostic system for a wide range of applications.

INTRODUCTION

Various biosensors and microarrays appeared in the late 1980’s as a major technological breakthrough, not the least due to the advanced use of photolithography process applied to the implementation of biochips and progress in surface chemistry, biology, microfluidics, instrumentation, electronics, optics and bio-informatics [1]. Technologies that are employed at each step should be versatile enough to adapt to different challenges and needs, depending on the application in mind.

According to a new technical market research report “Microsensors: MEMs, Biosensors and Nanosensors” (IAS027A) from BCC Research, the global market for microsensors is expected to be worth $3.2 billion in 2008. This will increase to over $8.4 billion by the end of 2013, a compound annual growth rate (CAGR) of 21.3%. The biochips market segment was worth $465 million in 2007 and will reach $581.5 million in 2008. It is expected to increase to $1.8 billion by the end of 2013, for a CAGR of 25.6%. Nanosensors are expected to see their first significant commercial sales in the years after 2008, reaching almost $159.9 million by 2013 [2]. However, micro and nanosensors technologies are still at the research and development stages, and their eventual commercialization will require the commitment of substantial resources, with long payback periods and substantial financial risk.

Diabetes is a worldwide public health problem. This metabolic disorder results from insulin deficiency and hyperglycemia and is reflected by blood glucose concentrations outside the normal range of 80-120 mg/dL. The complications of battling diabetes are numerous. The diagnosis and management of diabetes requires a tight monitoring of blood glucose levels. Accordingly, millions of diabetics test their blood glucose levels daily, making glucose the most commonly tested analyte. It was estimated that the glucose biosensors account for about 85% of the entire biosensor market [3]. There are over 40 commercially available devices for home testing of blood glucose levels, but over 90% of this market consists of products manufactured by four major companies, including Life Scan, Roche Diagnostics, Abbott, and Bayer [3].

The measurement of the pH values needs to be accurate and instant in ever-increasing range of applications. The value of pH has significant kinetic and thermodynamic effects on biochemical reactions since H⁺ reacts rapidly with metabolites forming near-equilibrium mixtures of dissociated anions and undissociated acid forms of the metabolite [4]. Muscle pH can be used to triage and help treat trauma victims and indicate poor peripheral blood flow in diabetic patients.

The earliest method of pH measurement was by means of chemical indicators, e.g. litmus paper that changes its colour in accordance to a solution. The most popular potentiometric approach utilise glass electrode because of its high selectivity for hydrogen ions in a solution, reliability and straightforward operation. Ion selective membranes, ion-selective field effect transistors, two terminal microsensors, fibre optic and fluorescent sensor, polymer and metal oxides based conductimetric pH-sensing devices have also been developed [5, 6, 7, 8, 9].

ISFET is a potentiometric pH sensor that is easily adapted to a wide range of chemical, biochemical and biomedical measurements. The operation of this sensor is based on the surface adsorption of charges from the solution under test in the solid-electrolyte interface that is part of the gate of the ISFET. As a result of this process, the threshold voltage of the ISFET is modulated [10].

The research on miniaturized polymer based pH sensors has recently emerged due to advances made in the properties of polymer materials, where mixing various polymers or adjusting the technological parameters can tailor the sensitivity to pH [8].

Potentiometric pH measurement using a neutral carrier membrane placed on a conducting polymer was employed by [11]. This device was one of the earliest tested in vivo pH and glucose sensors, manufactured using thin film technology on flexible polymer substrate.

Although self-testing is considered a major advance in glucose monitoring, it is limited by the number of tests per day and by inconvenience associated with standard finger-stick sampling, which deters patients from frequent self-monitoring [3]. Moreover, such testing neglects the monitoring of night time variations and tighter glycemic control through continuous monitoring is desired for detecting sharp changes in glucose level and triggering a proper alarm in cases of hypo- and hyperglycemia. Implantable nanoscaled sensors are envisaged as forthcoming solution to this issue [7].

The research towards integration of multi-sensor head for simultaneous in vivo monitoring is ongoing.
EXPERIMENTAL PROCEDURE

Figure 1 depicts the CAD layout of the microsensors arrays electrodes (top); and closer look at the structure of individual sensor with interdigitated electrodes (bottom).

The process for the manufacture of microscaled interdigitated electrodes for sensors array was as follow. A p-type silicon wafer was utilized, on top of which 1 µm silicon oxide layer was thermally grown using a Thermco 9000 furnace. Then the photoresist (a bi-level resist system with Micro-chem LOR3A and Shipley S1813) was spun on using a Laurell WS-400A spinner. This resist was exposed using a Karl-Suss MA1006 mask aligner. Resist was developed in a bath of Microposit MF319 developer. After undeveloped resist was rinsed off, a deposition of 200 nm gold using a Temescal FC-2000 E-beam evaporator was performed. Afterwards, the photoresist was etched in a bath of Microposit 1165 resist-stripper, which resulted in lifting-off the gold on the photoresist, but leaving the gold electrodes on the oxide.

At the next stage a PECVD deposition of 200 nm silicon nitride using an STS PC310 took place. Subsequently, a photoresist (Shipley S1813) was applied, exposed and developed (Microposit MF319). Then nitride was plasma etched using the photoresist as hard mask with an STS ICP etcher. Figure 2 illustrates SEM image of the resultant electrodes arrays, whereas Figure 3 depicts the interdigitated electrodes structure of an individual sensor within the array. The width of each electrode is 2 µm.

Novel nanopatterning technology offered by BioForce NanoeNabler™ was successfully tested for developing various nano sensors arrays. This system uses a liquid dispensing process via specially designed surface patterning tool (SPT), which is microfabricated cantilever with an integrated passive microfluidic system.

Fluid loaded into the reservoir flows down the microchannel by capillary flow until it reaches the gap at the end of the SPT [12]. During the deposition process, which typically takes less than 100 msec, SPT end touches the surface and a volume of fluid is instantly transferred. The NanoeNabler™ can deliver attoliter to picoliter volumes of liquid with a high degree of spatial accuracy. It is strongly believed that the reduction in the size of surface immobilized assays creates new opportunities in areas of chemical and biological sensor development [13].
The operation of the sensing elements is based on the properties of polymers, which exhibit a change in their electrical characteristics (such as conductivity, potential or capacitance), on exposure to solutions with different concentrations of pH value \([8, 7, 9, 14]\). A number of different polymers can be used to form the sensor arrays (fabricated using novel technology offered by BioForce NanoNabler™), with each array element having unique selectivity and sensitivity properties.

**RESULTS AND DISCUSSIONS**

The outcome of a number of projects undertaken by the Micro Electronics and Semiconductor Research Centre in the University of Limerick, Ireland resulted in development of real-time monitoring systems for pH, water quality, pressure, humidity, gas, ozone, radiation and so forth \([9, 14, 15, 16]\). Current efforts are towards miniaturization of these previously developed sensors systems to micro and nanoscale level using novel nanopatterning technology. For example, a nanotechnology-based sensors system is being developed to detect and monitor the quality of food. Attention is focused on one type of bacteria group, namely the Bacillus cereus group, which is commonly found in liquid, milk powder and mixed food products \([17]\). An array of sensors is used to achieve more accurate reading results. The sensor materials used for bacteria detection were prepared based on polyaniline (PANI) (emeraldine salt) grafted to lignin, polyethylene adipate (PEA) and hypermer PS3 in various proportions \([17]\).

Electrochemical methods of glucose detection are usually based on the glucose oxidase (GOx)-catalyzed oxidation of glucose, producing gluconic acid and hydrogen peroxide with the consumption of oxygen \([18]\). The measured signal is derived from the electrochemical oxidation of hydrogen peroxide or reduction of oxygen at a fixed electrode potential.

Fig. 3 presents optical images of 3 various sensor arrays, manufactured using different pH-sensitive solutions based on conducting polymer compositions of PANI, PS3 and Polyvinyl Butyral (PVB). The properties of the materials, as well as humidity, surface properties and other parameters would affect the final dimension of each sensor head. Once the proper parameters are chosen, the process of microsensors arrays manufacture is fast, reliable and highly consistent, which is extremely important for the biomedical applications.

There are a number of parameters that have to be considered when using the BioForce nanopatterning technology to achieve reproducible results over a big scale. Material-substrate interaction is vital and patterning surface should be hydrophilic. This was achieved by UV-ozone surface treatment. The following substrates were tested: Si coated with Au, alumina, glass and transparent polymer substrate. Additionally, polymer/solvent composition has been adjusted to allow uniform patterning.

![Figure 3](image-url)
Cloarec J-P et al [1] recently reported routine manufacture of arrays of hydrophilic spots of 500 µm in diameter with a centre to centre pitch of 750 µm. However, general difficulties with the control of the dimensions of spots for the printing process were highlighted [1].

The properties of materials are the key parameter that effect sampling rates, recovery times and so forth. The strategy of simultaneous measurement of a number of sensor arrays relies on the application of pattern recognition techniques, similar to the one in e-nose systems, which could be developed once the properties of suitable sensing polymers are characterized [19].

The above-described methodology for the fabrication of nanosensors arrays may be extended to surface patterning of a broad spectrum of various nanoscale materials and thereby create opportunities in a variety of fields ranging from microelectronics to bio/nanotechnology [20].

CONCLUSION

The method for microsensors arrays manufacture using BioForce NanoNabler™ was successfully employed to achieve miniaturization of previously developed pH and glucose sensors for real-time monitoring systems.

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