Fabrication and Characterization of Silicon Based Vertical Electrode Nanogap Biosensor for Protein Detection

By

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FABRIKASI DAN PENCIRIAN PENDERIA-BIO SELA-NANO ELEKTROD TEGAK BERDASAR SILIKON UNTUK PENGESANAN PROTEIN

ABSTRAK

Penderia-bio sela-nano merupakan peranti kelas baru yang telah menarik perhatian dan minat yg mendalam di kalangan penyelidik diatas potensi mereka di dalam aplikasi nanoteknologi. Peranti sela-nano ini yang difabrikasi menggunakan teknologi piawai Semikonduktor Komplimentari Logam Oksida (CMOS), mempunyai potensi untuk beroperasi sebagai simpang bio-molekul berikutan saiznya yang mengurangkan kesan pengutuban elektrod dengan menghiraukan frekuensi. Teknologi simpang ini adalah sistem penukar biologi-kepada-digital yang membolehkan penukaran masa nyata isyarat dielektrik bio-molekul kepada maklumat digit. Penderia-bio sela-nano ini mengandungi elektrod substratum silikon yang didop berat dan elektrod polisilikon yang dipisahkan secara tegak oleh peruang silikon oksida dengan jarak tetap 80nm. Pembangunan proses aliran di dalam penyelidikan ini mengandungi parameter – parameter dan resipi – resepi terperinci untuk menakrif peruang sela-nano ini. Dua (2) jenis topeng kerintangan digunakan di dalam proses ini iaitu Topeng Kerintangan Elektrod dan juga Topeng Kerintangan Pad Aluminium. Kedua – dua topeng kerintangan ini direkabentuk menggunakan perisian AutoCAD dan rekabentuknya dipindahkan ke atas topeng keringatan jenis lutsinar. Fokus utama penyelidikan ini ialah untuk menghasilkan peruang sela dengan menggunakan kaedah Plasma Terganding Beraruhan – Pemunar Ion Bertindak Balas (ICP – RIE) untuk memunar lapisan polisilikon dan asid hidroflorik (HF) penimbal untuk memunar lapisan silikon oksida. Walau bagaimanapun, silikon oksida tersebut tidak dipunar sepenuhnya, supaya lapisan yang tertinggal akan bertindak sebagai peruang sela mekanikal. Langkah terakhir melibatkan proses pemercitan dan pencorakkan aluminium ke atas pad sentuh menggunakan teknik piawai litografi-foto. Ini dilakukan untuk membantu mengurangkan kebolehubahan di dalam rintangan sentuhan apabila peranti sela-nano ini dikuarkan. Matlamat utama di dalam penyelidikan ini adalah untuk merekabentuk, memfabrikasi, menciri, dan menguji penderia-bio sela-nano elektrod tegak berdasar silikon yang akan digunakan untuk mengesan protein sasaran di dalam larutan berair.

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FABRICATION AND CHARACTERIZATION OF SILICON BASED VERTICAL ELECTRODE NANOGAP BIOSENSOR FOR PROTEIN DETECTION

ABSTRACT

The nanogap biosensor is a new class of device that has attracted attention and great interest among the researchers due to their potential applications in nanotechnology. This nanogap device which are fabricated using standard Complimentary Metal Oxide Semiconductor (CMOS) technology, have the potential to serve as the biomolecular junctions because their size reduces electrode polarization effects regardless of frequency. This junction technology is essentially a biology-to-digital converter system that enables real time conversion of biomolecular dielectric signals into digital information. This nanogap biosensor consists of a heavily doped silicon substrate electrode and poly-silicon electrode vertically separated by a fixed distance of 80 nm silicon oxide spacer. The process flow development in this research consists of detailed parameters and recipes to define the nanogap spacer. Two (2) types of masks are used in the process which are the Electrode Mask and the Aluminum Pad Mask. Both masks are designed by using the AutoCAD software and transferred onto a transparency. The main focus in this research is to create the gap spacer by using Inductive Coupled Plasma – Reactive Ion Etch (ICP- RIE) to etch the poly-silicon layer and buffered hydrofluoric acid (HF) to etch the silicon oxide layer. However, the silicon oxide was not completely etched, so that the remaining will act as the mechanical spacer gap. The final step involved sputtering and patterning aluminum onto contact pads using a standard photolithography technique. This was done to help minimize the variability in contact resistance when the nanogap device was probed. The overall goal of this research is to design, fabricate, characterize, and test the silicon based vertical electrode nanogap biosensor that will be used to detect and identify target proteins in aqueous solution.

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GLOSSARY OF ABBREVIATIONS

AFM	=	Atomic Force Microscope
AR	=	Anti Reflective
BAPP	=	Beta-Amyloid Precursor Protein
BOE	=	Buffered Oxide Etch
BSE	=	Bovine Spongiform Encephalopathy
CD	=	Critical Dimension
CJD	=	Creutzfeldt-Jakob Disease
CMOS	=	Complementary Metal Oxide Semiconductor
DI	=	Dionized
DNA	=	Deoxyribonucleic Acid
DS	=	Dielectric Spectroscopy
EBL	=	Electron Beam Lithography
EDL	=	Electric Double Layer
ELISA	=	Enzyme-Linked Immunosorbent Assay
EUV	=	Extreme Ultraviolet Lithography
HCL	=	Hydrochloric Acid
HF	=	Hydrofluoric Acid
HPM	=	High Power Microscope
HNO_3	=	Nitric Acid
ICP-RIE	=	Inductive Coupled Plasma-Reactive Ion Etching
KOH	=	Potassium Hydroxide
LPCVD	=	Low Pressure Chemical Vapor Deposition
NH_4F	=	Ammonium Fluoride
PECVD	=	Plasma Enhanced Chemical Vapor Deposition
PVD	=	Physical Vapor Deposition (Aluminum Evaporator)
QM	=	Quantum Mechanics
RIE	=	Reactive Ion Etching
RNA	=	Ribonucleic Acid

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SC	=	Standard Cleaning
SEM	=	Scanning Electron Microscope
SOI	=	Silicon on Insulator
SPA	=	Semiconductor Parameter Analyzer
STM	=	Scanning Tunneling Microscope
TMAH	=	Tetramethyl Ammonium Hydroxide

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CHAPTER 1

BACKGROUND

1.1 Introduction

Understanding the relationship between protein structure and its function is paramount to unlocking life's processes on a molecular scale, and it is important to develop efficient measurement tools necessary to record these relationships. Previously, researchers have extensively developed Deoxyribonucleic acid (DNA) chips for gene expression profiling and mutation mapping (Thomas, Hopkins, & Brady, 1998; Chang et al., 2007) over the past decade as seen in Figure 1.1. Wang et al. (2001) have reported electrochemical detection of DNA using magnetic particles for separation and concentration of target DNA.

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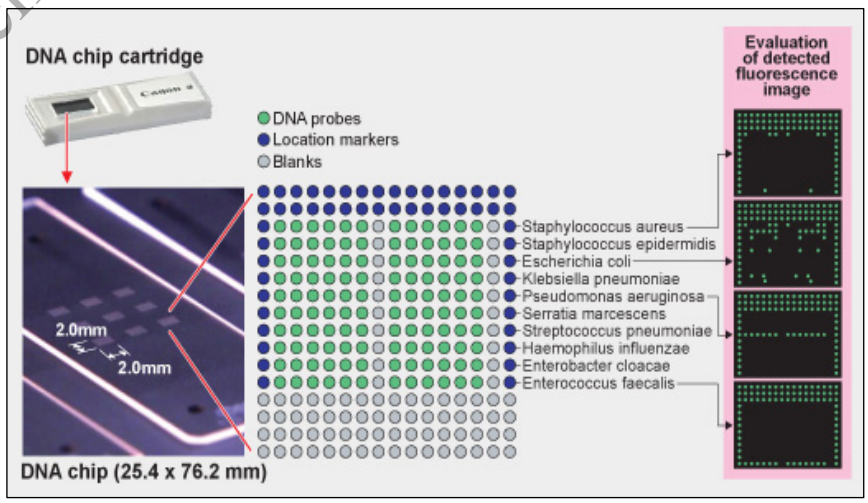

Figure 1.1: Example of a DNA Chip for Infectious Disease Diagnosis ("DNA Chip Fabrication Technology", 2008)

Since the activity of encoded proteins can directly manifest gene function (Emili, & Cagney, 2000) and plays an essential role in molecular biological analysis (Kelvin, 2001), researchers and scientists must develop a protein biochip or biosensor that can identify target proteins and provide information that is useful to many medical applications including the diagnosis of cancer in the early stage and drug discovery.

The basic construction concept of a protein chip, as seen in Figure 1.2, is somewhat similar to the DNA chip because it has a glass, plastic, and a silicon oxide surface immobilized with bio-molecules (Chang et al., 2007). Bio-molecules functional magnetic particles have been extensively applied in various bioelectronic applications.

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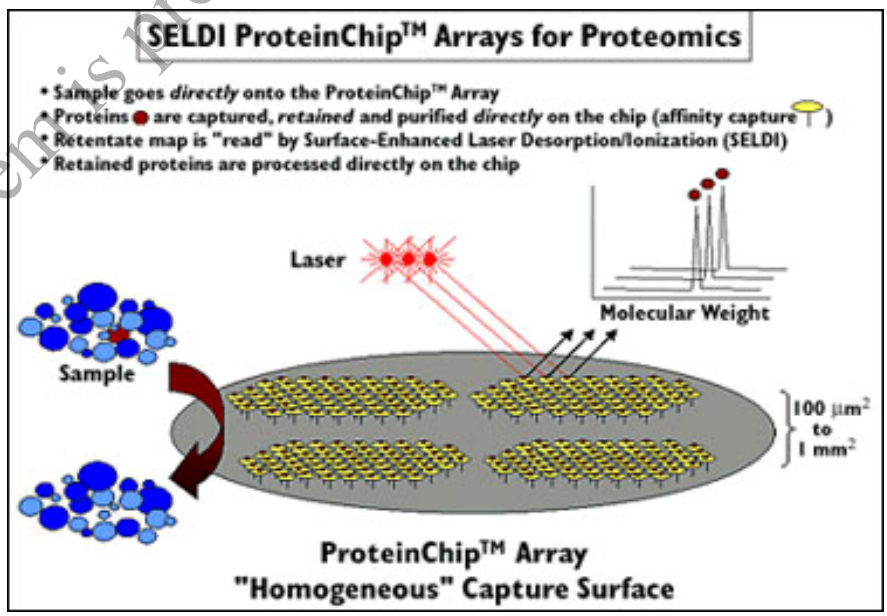

Figure 1.2: Example of a protein chip (DeFrancesco, 1999)

These bio-molecules are the fundamental building blocks of living cells such as double stranded DNA, protein structure and antibodies. The bio-molecules have been electrically characterized predominantly by a single or few molecule experiments (Joachim, 2000; Mayor, 2003; Ruttkowski et al., 2005). Specific junctions between the cells of these bio-molecules conduct electrical and chemical signals that result from various kinds of stimulation. The output signals will provide information of normal functions of the cells such as energy storage, information storage and retrieval, tissue regeneration, and sensing (Frank, n.d).

In this chapter, an overview of biosensors and biomolecules will be presented, and the discussion continues with the objectives of this research, the research scope, the problem statement and lastly the whole dissertation layout of this thesis.

1.2 Overview of Biosensor

A biosensor is an analytical device which converts a biological response into an electrical signal as seen in Figure 1.3. The term biosensor is often used to cover sensor devices used in order to determine the concentration of substances and other parameters of biological interest even when they do not utilize a biological system directly (Chaplin, 2004).

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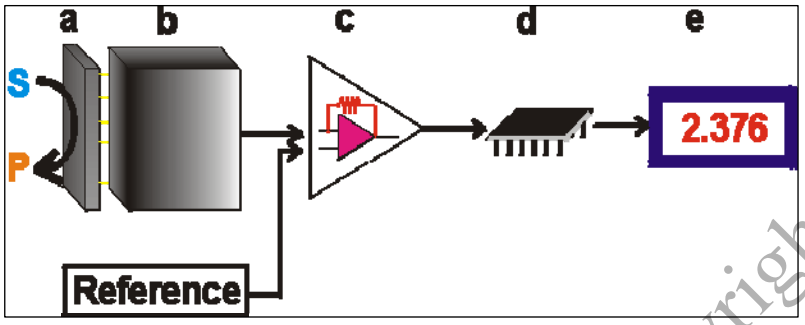

Figure 1.3: Schematic diagram of main components of biosensor (a) biocatalyst (b) transducer (c) amplifier (d) processor (e) display (Chaplin, 2004)

Many of today's biosensor applications are similar, in that they use organisms which respond to toxic substances at a much lower level than human to warn us of their presence. Such devices can also be used in both environmental monitoring and water treatment facilities (Chaplin, 2004).

Biosensors have the potential to affect many areas. Field application areas including medicine, physical therapy, music, and the video game industry, can all benefit from the introduction of biosensors (Tonnesen, & Withrow, 2008). The most widespread example of a commercial biosensor is the blood glucose biosensor, which uses an enzyme to break blood glucose down.

Biosensors are typically classified by the type of recognition element or transduction element employed. A sensor might be described as a catalytic biosensor if its recognition element comprised an enzyme or series of enzymes, a living tissue slice (vegetal or animal), or whole cells derived from microorganisms such as bacteria, fungi, or yeast. The sensor might be described as a bio-affinity

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sensor if the basis of its operation were a bio-specific complex formation. Accordingly, the reaction of an antibody with an antigen or hapten, or the reaction of an agonist or antagonist with a receptor, could be employed. In the former case, the sensor might be called an immunosensor (Tonnesen, & Withrow, 2008).

There are three basic principles of detection of biosensors. Optical biosensors which are based on the phenomenon of surface plasmon resonance are evanescent wave techniques. This utilizes a property shown of gold and other materials, specifically that a thin layer of gold on a high refractive index glass surface can absorb laser light, producing electron waves on the gold surface ("Biosensors – Application and How Multiwalled Carbon Nanotubes Are Used In Sensor Production", 2008).

Electrochemical biosensors are normally based on enzymatic catalysis of a reaction that produces or consumes electrons where such enzymes are rightly called redox enzymes. The sensor substrate usually contains three electrodes, a reference electrode, an active electrode and a sink electrode. The target analyte is involved in the reaction that takes place on the active electrode surface, and the ions produced will create a potential which is subtracted from that of the reference electrode to give a signal (Yvon, 2008).

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Piezoelectric sensors utilize crystals which undergo an elastic deformation when an electrical potential is applied to them. An alternating potential produces a standing wave in the crystal at a characteristic frequency. This frequency is highly dependent on the elastic properties of the crystal, such that if a crystal is coated with a biological recognition element the binding of a large target analyte to a receptor will produce a change in the resonance frequency, which gives a binding signal (Chaplin, 2004).

The quality of the results obtained from sensors based on biological recognition elements depends most heavily on their ability to react rapidly, selectively, and with high affinity. Antibodies and receptors frequently react with such high affinity that the analyte does not easily become unbound. To reuse the sensor requires a time-consuming regeneration step. Nonetheless, if this step can be automated, semi continuous monitoring may be possible (Yvon, 2008).

1.3 Problem Statement

Over the past years, several groups have reported on carbon nanotube, semiconductor nanowire chemical (Kong et al., 2008; Steuermann et al., 2002), and biomolecular sensors (Kong et al., 2008; Steuermann et al., 2002; Cui, Wei, Park, & Lieber, 2001). The biosensing applications are in many ways, driven by the emerging concepts of system biology (Davidson et al., 2003; Kitano, 2002) and the translation of those concepts into the clinic (Hood, Heath, Phelps, & Lin, 2004)

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Chip-based methods for the detection of Ribonucleic acid (RNA) (Fodor et al., 1991), DNA and proteins (Macbeath, & Schreiber, 2000) are now part of most experimental biology toolset. As a general rule, the chip-based methods are predicted upon the optical detection of specific biomolecules through the use of fluorophore labeling technique. The proto-typical example for quantitative peptides, proteins and antibodies is the technique known as Enzyme-Linked Immunosorbent Assay (ELISA) as seen in Figure 1.4, which is the most popular method for disease detection due to its simplicity and high sensitivity.

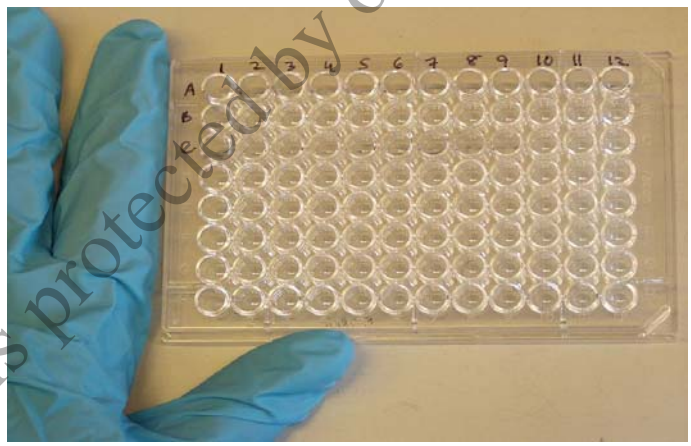

Figure 1.4: A 96-well microtiter plate being used for ELISA (Mugirya, 2006)

Despite the popularity, ELISA suffers several limitations where its detection method is not real time, the intensity of the product needs to be measured by an expensive optical device, and experienced operators must perform the ELISA to obtain accurate results (Chang et al., 2007). This kind of instrumentation is also bulky, costly and not portable.

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