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DESIGN, FABRICATION AND CHARACTERIZATION OF SILICON NANOWIRE-BASED DNA BIOSENSOR FOR DENGUE VIRUS DNA DETECTION

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By

SITI FATIMAH BINTI ABD RAHMAN

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

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DESIGN, FABRICATION AND CHARACTERIZATION OF SILICON NANOWIRE-BASED DNA BIOSENSOR FOR DENGUE VIRUS DNA DETECTION

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August 2016

Chairman : Professor Nor Azah Yusof, PhD
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Silicon nanowire (SiNW) has attracted significant interest because of its potential applications from nanoscale electronics to biomedical engineering. The SiNW represent an important class of materials with unique features such as identical diameters to biomolecules, applicable to apply in biomolecule or chemical detection and can be fabricated as highly sensitive biosensor device. Thus, this study demonstrates the development of SiNW biosensor for detecting deoxyribonucleic acid (DNA) of dengue virus utilizing electron beam lithography (EBL) coupled with conventional lithography (CL) for device fabrication. The surface of fabricated SiNW is chemically modified using 3-aminopropyltrieloxysilane (APTES) in order to transform the devices as a functional sensing element. Prior to biomolecule testing, the amine-terminated SiNW device is first evaluated in response to the pH level detection for optimizing the sensor sensitivity that related to the effect of SiNW width and SiNW number. It was found that, the device consist of single SiNW with 60 nm in width shows the highest sensitivity as compared to those devices consists of larger SiNW and in array formation as well. The optimized SiNW device is then employed for the detection of dengue virus DNA by introduced the additional of three-step procedure involving glutaraldehyde surface treatment, DNA immobilization and DNA hybridization. Contact angle measurement, fourier transform infrared spectroscopy (FTIR) and x-ray photoelectron spectrometry (XPS) are used to assess the effectiveness of the attachment protocol. The detection principle works by detecting the changes in the electrical current of SiNW which bridge the source and drain terminal to sense the immobilization of probe DNA and their hybridization with target DNA. The oxygen (O_2) plasma is proposed as an effective strategy for increasing the binding amounts of target DNA by modified the SiNW surface. It was found that the detection limit of the 60 sec plasma treated-SiNW device could be reduce to 1.985 x 10^{-14} M as compared to 4.131 x 10^{-13} M for the untreated-SiNW device with a linear detection range from 1.0 x 10^{-9} M to 1.0 x 10^{-13} M of complementary target DNA. In addition, the developed biosensor device was able to discriminate between complementary, single mismatch and non-complementary DNA sequences. This highly sensitive assay is also able to detect reverse transcription-polymerase chain reaction (RT-PCR) product of

dengue virus DNA in real samples, making it as a potential method for disease diagnosis through electrical biosensor detection.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

REKA BENTUK, PEMBANGUNAN DAN PENCIRIAN SILIKON NANOWAYAR-BERDASARKAN DNA BIOPENDERIA UNTUK PENGESANAN DNA DENGGI VIRUS

Oleh

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Silikon nanowayar (SiNW) telah menarik minat yang ketara dalam kajian ini kerana ia berpotensi untuk diaplikasi daripada elektronik skala nano sehingga kejuruteraan bioperubatan. SiNW merupakan suatu bahan yang terpenting dengan ciri-ciri uniknya seperti diameter serupa dengan biomolekul, membolehkan untuk digunakan dalam pengesanan biomolecule atau kimia dan boleh dibuat sebagai peranti biopenderia yang sangat sensitif. Oleh itu, kajian ini menunjukkan proses pembangunan biopenderia SiNW untuk mengesan asid deoksiribonukleik (DNA) denggi virus dengan menggunakan kaedah litografi alur electron dan litografi konvensional dalam penghasilan alat peranti. Untuk berfungsi sebagai elemen penderia, permukaan SiNW diubahsuai secara kimia dengan menggunakan 3-aminopropiltrielosilen (APTES). Sebelum ujian biomolekul, sensitiviti peranti yang berkaitan dengan kesan lebar SiNW dan bilangan SiNW dioptimalkan berdasarkan tindak balas kumpulan amina-SiNW kepada pengesanan tahap pH. Didapati bahawa, peranti yang terdiri daripada SiNW tunggal dengan kelebaran sebanyak 60 nm menunjukkan sensitiviti yang tertinggi berbanding dengan peranti-peranti lain yang terdiri daripada SiNW bersaiz besar dan dalam kuantiti yang banyak. Kemudian, tiga-langkah prosedur iaitu pengubahsuaian menggunakan glutaraldehid, DNA immobilisasi dan DNA hibridisasi telah dilakukan ke atas alat peranti SiNW yang terpilih. Alat pengukuran sudut, spektroskopi inframerah transformasi fourier dan spektroskopi fotoelektron sinar-x digunakan untuk menilai keberkesanan protokol yang dijalankan. Kaedah pengesanan DNA immobilisasi dan DNA hibridisasi dijalankan berdasarkan perubahan arus elektrik SiNW yang menjadi penghubung antara pangkalan sumber dan pangkalan salir alat peranti. Pengubahsuaian SiNW menggunakan oksigen plasma didapati menjadi strategi yang berkesan untuk meningkatkan jumlah pelekatan DNA sasaran. Had pengesanan alat peranti yang mempunyai SiNW diubahsuai oleh plasma selama 60 saat boleh dikurangkan kepada 1.985×10^{-14} M berbanding 4.131×10^{-13} M untuk peranti SiNW yang tidak diubahsuai dengan julat pengesanan DNA jujukan-sepadan iaitu dari 1.0×10^{-9} M sehingga 1.0×10^{-13} M. Selain itu, alat peranti biopenderia yang dibangunkan dapat menunjukkan perbezaan antara DNA pelengkap, DNA tidak sepadan tunggal dan DNA bukan

pelengkap. Alat peranti yang sangat sensitif ini juga boleh mengesan DNA virus denggi dalam sampel sebenar iaitu produk dari reaksi rantai polimerase-transkripsi terbalik (RT-PCR), menunjukkan bahawa kaedah ini berpotensi sebagai alat diagnosis penyakit melalui pengesanan biopenderia secara elektrik.

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I certify that a Thesis Examination Committee has met on 10 August 2016 to conduct the final examination of Siti Fatimah binti Abd Rahman on her thesis entitled "Design, Fabrication and Characterization of Silicon Nanowire-Based DNA Biosensor for Dengue Virus DNA Detection" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Acc. Voltage	Accelerating voltage
AFM	Atomic force microscope
APTES	3-aminopropyl-triethoxysilane
Au	Aurum
AuNP	Gold nanoparticle
BF	Bright field
BOX	Buried-oxide
CMOS	Complementary metal-oxide-silicon
CVP	Chemical vapor deposition
DI	De-ionized
DF	Dark field
DNA	Deoxyribonucleic acid
dsDNA	Double-stranded dna
EBL	Electron beam lithography
FET	Field effect transistor
FTIR	Fourier transform infrared spectroscopy
GA	Glutaraldehyde
GDS II Editor	Graphic display system ii editor
H_2	Hydrogen
HPM	High power microscope
ICP-RIE	Inductive coupled plasma-reactive ion etching
ISFET	Ion-selective field effect transistor
I-V	Current-voltage
LPM	Low power microscope

NW	Nanowire
O_2	Oxygen
PBS	Phosphate buffer silane
PR	Photoresist
PVD	Physical vapor deposition
RIE	Reactive ion etching
RT-PCR	Reverse transcription-polymerase chain reaction
SEM	Scanning electron microscope
Si	Silicon
SiH_4	Silane
SiNW	Silicon nanowire
SiO_2	Silicon dioxide
SiOH	Silanol
SMU	Source measurement units
SOI	Silicon-on-insulator
ssDNA	Single-stranded DNA
TEM	Transmission electron microscopy
Tm	Melting temperature
UV	Ultraviolet
VLS	Vapor liquid solid
XPS	X-ray photoelectron spectroscopy

CHAPTER 1

INTRODUCTION

1.1 Background

Biosensors have been in continuous development and improvement since their first appearance in 1962 (Dewa and Ko 1994). The genetic information brought by genome sequencing has attracted enormous efforts in the development of DNA biosensor (Baur et al. 2009). DNA biosensors consist of an immobilized DNA strand to detect the complementary sequence by hybridization process. The binding of the surface-confined probe and its complementary target strand is translated into a useful electrical signal (Wang 2002).

The hybridization process between the probe and its complementary sequence can be determined by several transduction methods that have been reported in the literature included optical, electrical, electrochemical and gravimetric devices (Grieshaber et al. 2008; Monosik et al. 2012). Some of this detection requires a label such as magnetic beads, metal complexes, organic redox marker or intercalators to attach with the DNA target (Baur et al. 2009; Berdat et al. 2006). Although the labeling step enhances the sensor sensitivity, however, the labeling-based detection markedly increases the time, complexity and cost of the measurement (Baur et al. 2009; Teles and Fonseca 2008).

For these reasons, enormous efforts were made in the development of simple, portable, rapid and label-free devices suitable for sequence-specific DNA detection. These criteria have been accomplished by using an electrical biosensor for DNA hybridization detection (Monosik et al. 2012). In 1997, Souteyrand and co-workers pioneered in the development of DNA hybridization detection by using a field effect transistor (FET) sensor. The operational dimensions of the device were reported in millimeter range, with recording buffer concentrations in the order of a milimole (Souteyrand et al. 1997).

The integration of nanomaterials into device structures for biosensing applications has played a central role in the development of new strategies for signal transduction (Noor and Krull 2014). Due to comparable sizes of biological molecules and nanomaterials (as shown in Figure 2.1), the combination of nanomaterials with biomolecules offers potential for development of miniaturized sensing device for sensitive detection of biomolecules.

A wide range of nanoscale materials are promising candidates for biosensing application such as nanowire, nanotube and nanoparticle. Among them, silicon nanowire (SiNW) emerge as one of the best defined and controlled classes of the nanoscale building blocks, since SiNW is adaptable to the advantageously semiconductor-based technology (Lieber and Wang 2007). Silicon has been widely used in the development of biosensors, as it is biocompatible with semiconducting materials. The doping of silicon can be controlled whether developed by a lithography process based on a top-down approach or synthesized by chemical methods based on a bottom-up approach (Mohanty et al. 2012).

The SiNW is used in standard configuration of field effect devices which is connected to the metal source from where a current is injected and subsequently, it drains electrodes through which the current is collected. The current is moving in a path from source to drain electrode through nanowire, which is called a channel. The presence of a number of charged biomolecules on the surface of SiNW will induce a drastic change in the nanowire conductance (Lee et al. 2010). This can be demonstrated by taking an example of DNA molecules, as DNA strains possess net negative charge in aqueous solution. After specific binding to the linked molecules on the nanowire surface, it causes an increase in the surface negative charge. The increase in the negative surface charge will result in an accumulation of holes carrier in a p-type nanowire, thus an increase in conductance of the device will be observed (Arora et al. 2013). These field effect sensors can be used for detecting broad range biomolecules as well as chemical species based on nanowires surface modification with specific receptors.

In 2001, Cui group has introduced chemically-grown silicon nanowires (SiNWs) as a sensing element. The biotin-modified SiNWs were used to detect streptavidin down to a picomolar concentration range (Cui et al. 2001). Due to their small sizes and large surface-to-volume areas, SiNWs have demonstrated higher sensitivity detection as compared to the conventional planar-type biosensor based on the electrical detection. Hence, the SiNWs biosensors are based on the transduction of signals from biomolecules that enable direct electronic detection, which do not require any labeling steps. Comparing to optical and other electrochemical methods, the SiNWs based field effect sensor involve a much simpler detection method, easier setup and small size, which can be realized into the portable biosensor. This leads to the fast growing of the SiNWs as electrical field effect transducers which show significant advantages of label-free, rapid detection and highly sensitive biosensors (Hahm and Lieber 2004; Zhang et al. 2009; Zheng et al. 2005).

It was reported that, the existing SiNWs device synthesized by a bottom-up approach suffer from poorly in controlling nanowires diameter as well as the difficulty in precisely positioning to other existing microelectronic components (Zhang et al. 2001). The issues faced by these grown-up SiNWs have been overcome with the advent of SiNWs devices patterned by the top-down lithography. This approach allows the production of SiNWs with highly uniform, high reproducibility and well-aligned which can be easily integrated into electrical readout circuits (Poghossian and Schöning 2014). Thus, the top-down fabrication method by electron beam lithography (EBL) and integrated with the standard complementary metal-oxide-semiconductor (CMOS) process is implemented for device patterning in this research work.

Additionally, the intrinsic silicon oxide (SiO_2) surface of the SiNW can be easily and controllably modified with different probe molecules, which renders SiNW as direct and specific biosensors. Most of the methods reported used single-stranded DNA (ssDNA) probes, which have been selected from synthetic nucleic acid libraries as a receptor to hybridize with the target DNA (Zhang and Ning 2012). Simple synthesis, easy labeling, high stability and reusable after simple thermal melting of the DNA duplex have made the ssDNA molecules an ideal recognition probe for DNA hybridization detection (Ruslinda et al. 2013; Teles and Fonseca 2008). In order to provide the linking-site between nanowire surfaces to the recognition group of the ssDNA-probe, the SiO_2 is modified using chemical modification protocols. The 3-aminopropyltriethoxysilane (APTES) could be employed to chemical-link with the amine group of DNA molecules (NH_2-DNA) in combination with glutaraldehyde as a linker (Cui et al. 2001; Singh et al. 2010; Vercoutere and Akeson 2002), which is known as an established method for SiO_2/Si surface modification. Thus, this method has been employed in this research work in order to provide the linkage with the amine-terminated ssDNA-probe.

Central to the entire discipline of the formation of a DNA duplex on the SiNW surface is the concept of DNA hybridization. It is known that, the sensitivity of SiNW device is affected by binding amounts of target DNA (formation of DNA duplex) on the nanowire surface (Wu et al. 2013). Binding amount of target DNA could be improved by increasing the amounts of immobilized probe DNA. In this regard, much effort has been made on demonstrating nanostructures integrated on top of SiNW surface in order to increase the surface area of the device and thus increases the amount of analyte binding (Elfstrom et al. 2008; Ryu et al. 2010; Seol et al. 2012; Shao et al. 2008). Although the results of modified SiNW device with nanostructures are endowed with improved sensitivity, however, the comparable results can be obtained to increase the binding amounts of target DNA on the SiNW surface via oxygen (O_2) plasma surface treatment which has not widely studied is implemented in this research work. Without using a complex wet chemistry process to enhance the surface area of SiNW, the sensitivity of the sensor device is tunable simply by this method and the role of O_2 plasma treatment is elucidated.

1.2 Problem statement

Dengue illness is caused by the viruses of the Flaviviridae family and transmitted to human bodies by the Aedes aegypti mosquito that leads to dengue fever (DF) or its more severe case dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (Baeumner et al. 2002; Zhang et al. 2010). Today, dengue viruses have become a major public health concern and it is estimated to be 50 million infections per year with at least 22000 deaths (Zhang et al. 2010). To date, there is no specific treatment or an effective vaccine has yet to be developed to curing the disease. Mosquito eradication strategies have been taken as current prevention of the disease, which was reported with limited success (Baeumner et al. 2002). Thus, the reliable diagnostic method useful both for epidemiological surveillance and clinical diagnosis is required to identify the disease rapidly and accurately, and subsequently treat the dengue virus infection at the early stage (Guzmán and Kourí 2004).

The conventional method used for dengue virus infection diagnosis is based on detection of virus-specific antibodies, known as serological tests. One of the most common methods is enzyme-linked immunosorbent assay (ELISA), which is the detection based on immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to dengue virus (Lam and Devine 1998). IgM antibody is the first immunoglobulin isotype to appear and according to the Pan American Health Organization (PAHO) guidelines, by day five of illness, 80% of the cases have detectable IgM antibody. IgG can be detected in a low titer at the end of the first week of the infections and it will increase slowly (Guzmán and Kourí 2004; Peeling et al. 2010). In general, 10% false negative and 1.7% false positive reactions have been recorded by using this ELISA method (Guzmán and Kourí 2004). Even though this method has resulted in good approaching for routine dengue diagnosis, but it cannot give an early detection since this antibodies-based detection demands an appropriate time frame (after five days of onset of infections) in order to mount sufficient immune response to produce detectable antibodies in patients for diagnosis (Baeumner et al. 2002; Rahman et al. 2014).

More recently attention has been focused on molecular assays based on nucleic acid amplification for dengue virus detection. The molecular-based diagnostic assays such as reverse transcription-polymerase chain reaction (RT-PCR) is preferred as it is more sensitive and can provide reliable results in shorter assay time compared to serological techniques (Bhatnagar et al. 2012). The protocol however may increase the chance of sample cross-contamination and time-consuming due to the use of stained agarose gel electrophoresis for visualizing these fluorescent label detections (Lee et al. 2010). Furthermore, these techniques present a challenge for miniaturization due to a requirement of large and expensive instrumentation for complex nature of the detection systems, which include reverse transcription and thermal cycling steps (Li et al. 2009). Thus, there is a strong demand for a development of sensitive, label-free, fast response and portable sensing devices as replacements for the time-consuming, complexity and label-based assays.

From the point of view of the electrical properties, a conformational change in a biological or chemical event often causes the change in the electrical properties of the substances (Frederick 2005; Gao et al. 2007). Therefore, biosensors based on electrical detection could be more simple, rapid and portable detection platforms. The advancement of nanotechnology has opened up the opportunities of using electrical system for biomolecule. The SiNW has become a great candidate for use in miniaturized biosensors devices (Dresselhaus et al. 2007; Park et al. 2010) and have been proven as a powerful platforms for highly sensitive label-free detection of biological species, such as proteins (Cui et al. 2001), viruses (Patolsky et al. 2004) and DNA (Zhang et al. 2010). As sensing elements, SiNW has been studied to offer key advantages in the detection regime, which requires fast response, label-free method as well as the ability to detect target species with extremely low concentrations (Chua et al. 2009). These advantageous are significant for the development of molecular electronics based on SiNW device for early detection of Dengue diagnosis through DNA hybridization detection.

1.3 Research objective

The general objective of this study is to develop SiNW biosensor via top-down approach for DNA hybridization detection in dengue diagnosis application. The following specific objectives are designed to achieve the general objective:

i. To design, fabricate and characterize SiNW device using electron beam lithography (EBL) coupled with conventional photolithography process.
ii. To optimize the device sensitivity that consists of different SiNW width and SiNW number in response to the pH solution based on current-voltage (I-V) measurement.
iii. To characterize the chemically modified SiNW surface using fourier transform infrared spectroscopy (FTIR), water contact angle measurement and x-ray photoelectron spectroscopy (XPS).
iv. To examine the performance of the developed device for DNA of Dengue Virus detection based on electrically measurement of DNA hybridization events.
v. To evaluate the performance of the proposed SiNW biosensor device on the analysis of real sample (RT-PCR product of Dengue Virus).

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