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The Next Generation Biochip: The Development of Polysilicon Nanowire Effect Transistor Based Biosensor Array

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Abstract

We develop biosensing array chip that includes urgently needed functions of current biochip to face the growing demand in health care. By using polysilicon nanowire field effect transistor based biosensor assay, we demonstrate that the real-time, label-free and ultra-high sensitive detection of enzyme activities, nucleic acids and proteins can be achieved.

1. Introduction

Biochip in the form of microarray is an ingenious way to collect large amount of biochemical information. This method is especially suited for the current big data era when large amount of genomic and proteomic information are analyzed to answer many medical questions including aging, chronical diseases and personal medicine. However, applications of traditional biochip array are facing some major limitations, such as labeling requirement, specificity and sensitivity issues, and cost, which prevent many of its biomedical applications. Current technologies available in semiconductor and electronics industries may help to eliminate most, if not all, of these barriers.

Silicon nanowire field effect transistor (NWFET) has been demonstrated to function as a transducer for label-free, real-time at ultra-high sensitivity. Our research aims to develop such device that can be used for routine clinical application at affordable price. The fabrication of the NWFET must be fully compatible with commercial facilities at low cost and for mass production. This also implies that microarray with integrated circuit can become powerful addition to the NWFET based microarray biochip that requires the minima power usage. Furthermore, portable instrumentation can be developed. We are developing polysilicon nanowire field transistor (pSiNWFET) to meet all the above requirements for clinical and commercial applications in biomedical diagnosis.

In this report, we verified the electric properties and biosensing functions of pSiNWFET fabricated by low-cost commercial processes. Enzymatic reaction and a variety of nucleic acid and protein targets are examined to validate the function of pSiNWFET as a transducer for biosensing application. New pSiNWFET based biosensing methods, including miRNA, DNA methylation, single nucleotide polymorphism (SNP) are also developed. Our results indicate that the pSiNWFET biosensing system is promising for coming clinical application.

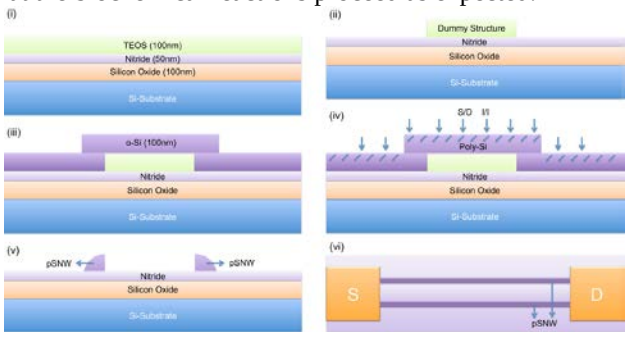
2. Methods

Fabrication of pSiNWFET- Scheme I illustrates key steps for the fabrication of pSiNWFET [1]. This method allows the preparation of polysilicon nanowire at low cost. The nanowire devices and chip were fabricated through commercial fab and provided by Helios Bioelectronics, Taiwan.

Determination of electric signals- The electric properties of the pSiNWFET and the changes of the signals during biosensing environments were determined by either I-V or lock-in methods [2].

Immobilization of bio-probes- The bio-probes on nanowires of the device were immobilized through silane and cross-linker. Similar procedures were used for both nucleic acid and protein/peptide probes. The processes were performed directly on the device surface, through microfluidic channel, or by an automatic spotting machine and confirmed through SEM and electric properties of the device [3].

Reactions on pSiNWFET- The reaction conditions on the nanowire surface were determined both in a traditional biochemical setup and in the pSiNWFET system to confirm that the biochemical reactions proceed as expected.



Scheme I Key steps for the fabrication of low-cost pSiNWFET commercially. Nanowires are formed by side-wall technique [1] and no expensive method is needed for the definition of the nanowires.

3. Results and Discussion

Commercial fabrication of pSiNWFET

The main purpose of this study is to develop low-cost pSiNWFET chip and accompanied instrumentation/methods that aim to meet unmet needs in molecular diagnosis through commercially compatible IC and semiconductor facilities. Fig. 1 shows the images of traditional biochip and a wafer that contains pSiNWFET arrays.

Biochemical reactions on pSiNWFET

Bio-probe immobilization can be monitored directly through the change of electric properties of the nanowire device as shown in Fig. 2. This phenomenon also explains one of the main differences between traditional biochip and the pSiNWFET based biochip (Fig. 1). The latter is a sensor array and the biochemical reactions can be directly monitored on pSiNWFET device as shown in Figs. 2 and 3.

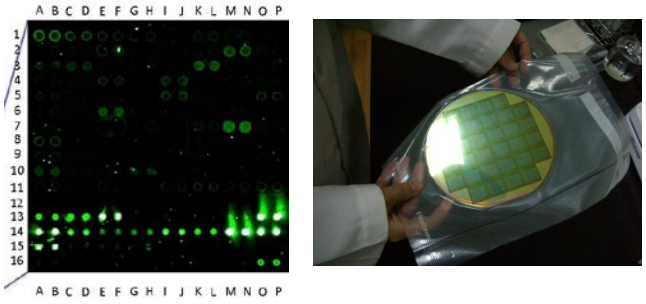


Fig. 1 Images of a traditional biochip (an *E. coli* proteome chip [4]) and wafer that contains pSiNWFET arrays chip.

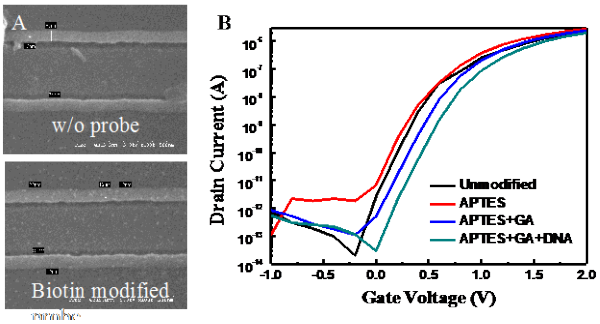


Fig. 2 Confirmation at each step of probe DNA immobilization by (A) SEM and (B) electric properties (I_D-V_G curves) [3].

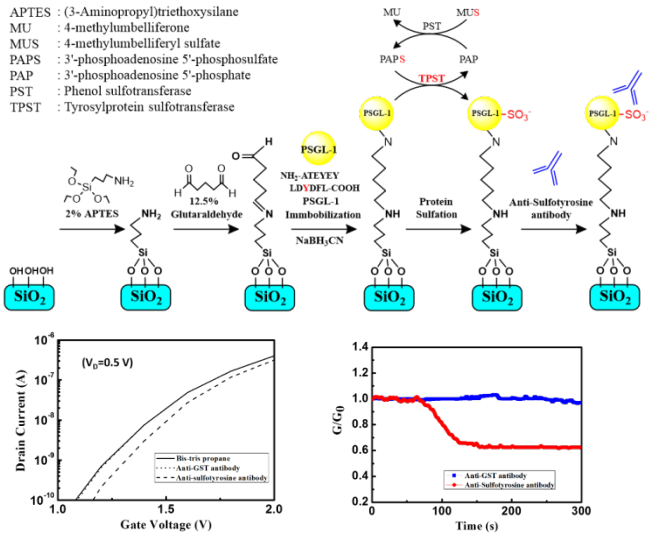


Fig. 3 Surface chemistry including immobilization of a peptide substrate, reaction of an enzyme catalyzed post-translational sulfation on the tyrosine [4], and recognition of the sulfated peptide by an anti-sulfo antibody (top). The interaction between antibody and the post-translationally modified peptide is directly monitored through I-V (lower left) and lock-in (lower right) methods [2].

Biosensing with proteins

Using commercial samples (General biologicals Co, Taiwan), Fig. 4 shows that the hepatitis B virus surface antigen (HBVs) can be detected at ultra-low concentration with anti-HBsAb antibody functionalized pSiNWFET.

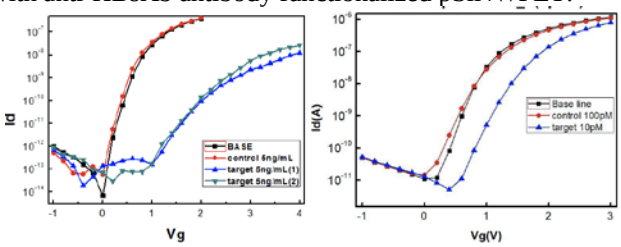


Fig. 4 Detection of HBVs with antibody at regular (5 ng, left panel) and low concentration (80 fg, right panel) of HBs.

Biosensing with nucleic acids

Identification of single nucleotide polymorphism (SNP) is shown in Fig. 5 as an example for nucleotide biosensing with pSiNWFET.

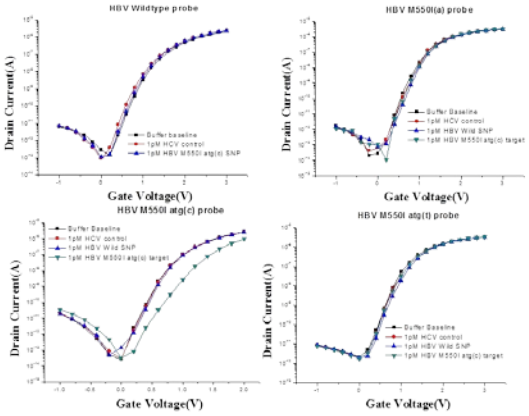


Fig. 5 Detection of SNP on DNA probe functionalized pSiNWFET. The target DNAs with a single mismatch give no change of electric signal. Only the fully complementary target DNA (lower left pane) gives significant shift of the I-V curve to the right.

4. Conclusions

The fabrication of the device, chip and accompanied detection system confirm that pSiNWFET is fully compatible with current commercial facilities and the nanowire devices can be reproducibly mass produced at low cost. The biosensing functions of the commercially fabricated devices have been demonstrated as expected at high efficiency even with biological samples. The development of pSiNWFET for clinical application is now in progress.

Acknowledgements

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