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# Silicon nanowire field-effect-transistor based biosensors: From sensitive to ultra-sensitive

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ABSTRACT

Silicon nanowire field effect transistors (SiNW-FETs) have shown great promise as biosensors in highly sensitive, selective, real-time and label-free measurements. While applications of SiNW-FETs for detection of biological species have been described in several publications, less attention has been devoted to summarize the conjugating methods involved in linking organic bio-receptors with the inorganic transducer and the strategies of improving the sensitivity of devices. This article attempts to focus on summarizing the various organic immobilization approaches and discussing various sensitivity improving strategies, that include (I) reducing non-specific binding, (II) alignment of the probes, (III) enhancing signals by charge reporter, (IV) novel architecture structures, and (V) sensing in the sub-threshold regime.



## 1. Introduction

A biosensor is generally defined as an analytical device, which converts the biochemical responses into the quantifiable electronic signals (Arlett et al., 2011; Malmqvist, 1993). Since Clark elucidated the first biosensor in the form of an enzyme electrode in 1962 (Clark and Lyons, 1962), extensive utility in medical diagnosis (Viswanathan et al., 2009), toxicity testing (Farre and Barcelo, 2003), chemical analysis (Wang et al., 2008), food industry (Rodriguez-Mozaz et al., 2006), and many other areas for quantitative assessments has appeared. A typical biosensor is composed of two interconnecting parts: the biological receptor (e.g. antibodies, enzymes, nucleic acids, etc.) and energy transducer (which working in an optical (Allsop et al., 2013; Haes and Van Duyne, 2002), piezoelectric (Garcia-Martinez et al., 2011), electrochemical (Britto et al., 1996; Kumar and D'Souza, 2011), electrical filed-effect (Cui et al., 2001) or other principle). The biological receptor is employed to identify the specific target molecule, and the transducer to transform the specific interaction of the analyte and the biological receptor into an optical or electronic signal. Various biosensing systems, such as optical spectroscopy (Allsop et al., 2013; Haes and Van Duyne, 2002), cyclic voltammetry (Britto et al., 1996; Kumar and D'Souza, 2011), impedance spectroscopy (Chen et al., 2013; Norouzi et al., 2011; Rodriguez et al., 2005), surface plasmon resonance (Deng et al., 2011; Ortiz et al., 2011; Wang et al., 2013), quartz crystal microbalance (Chen et al., 2010; Garcia-Martinez et al., 2011), and field-effect transistor based devices (Chen et al., 2011b; Cui et al., 2001; Stern et al., 2007) have been demonstrated to possess exceptional characteristics and outstanding performance while conjugated with the advanced nanotechnology. Improvements of these detecting systems are mainly due to the comparable sizes of the biological species, including proteins, nucleic acids, and even viruses or bacteria (Chen et al., 2011b). The binding of the biological specie onto the nano-biosensor is expected to significantly perturb the electrical properties of the nano-biosensor yielding a quantitative determination of analyte (Chen et al., 2011b; Elfstrom et al., 2007).

Several essential factors, such as sensitivity, specificity, and real-time monitoring, must be considered when one designs and fabricates nano-biosensors (Li et al., 2013b). In addition, to fulfill the need of pharmaceutical development and the diagnostic application, the potential of massive production of biosensor becomes another crucial factor. Among of various nano-biosensing techniques, silicon nanowire field-effect transistor (SiNW-FET), first reported in 2001 (Cui et al., 2001), has attracted more attention in relation to the matured semiconductor industry. Thus, massive production of SiNW-FET devices is readily conceivable (Chen et al., 2011b). Indeed, SiNW-FET has been demonstrated as ultra-sensitive sensors for real-time and label-free biomolecular detection of DNA (Bunimovich et al., 2006; Hahm and Lieber, 2004; Vacic et al., 2011; Wang et al., 2007), RNA (Zhang et al., 2009), proteins (Lin et al., 2010) (including cancer markers (Zheng et al., 2005)), viruses (Chiang et al., 2012; Patolsky et al.,

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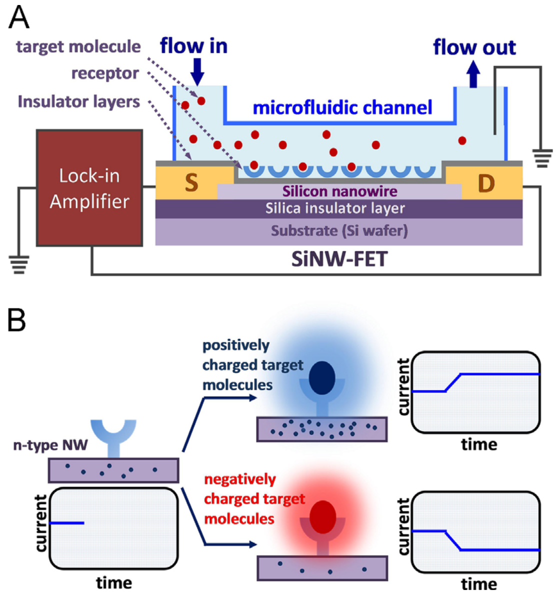


**Fig. 1.** Schematic illustrations of the working system and principle of the SiNW-FET biosensor. (A) A SiNW-FET is composed of a single SiNW (or a bunch of SiNWs), which is connected between a source (S) and drain (D) electrodes, laid on a Si wafer. The PDMS channel sitting on SiNW-FET device is utilized to deliver the sample. The electrical signal is typically recorded by a lock-in amplifier in the presence of water gate electrode (ex: Ag/AgCl reference electrode) directly inserts into the buffer solution. (B) Receptor molecules, immobilized on the SiNW(s), are utilized to recognize specific targets with a SiNW-FET biosensor. When positively charged targets bind on an n-type SiNW-FET, holes are accumulated in the SiNW leading to an increase in the electrical conductance. Conversely, negatively charged targets cause a depletion of charge carriers to reduce the conductance of SiNW.

2004), and other bio-species. In Fig. 1, a typical SiNW-FET device comprised of p/n-type single-crystalline SiNWs as conducting channels is illustrated, providing with the source (S) and drain (D) electrodes, and a gate electrode (a back gate electrode or a solution gate electrode).

"Top-down" (Stern et al., 2007) and "bottom-up" (Cui et al., 2001) are two major fabrication techniques used for the SiNW-FETs preparation. The "top-down" SiNW-FETs are fabricated from silicon-on-insulator (SOI) wafer (Lin et al., 2007) by lithographic processes combined with electron-beam etching and doping technique to define the SiNWs (light doping) and S/D electrodes (heavy doping). On the other hand, the process to prepare "bottom-up" SiNW-FETs usually starts from the growth of SiNWs in a chemical vapor deposition (CVD) system (Zheng et al., 2004). With the nano-crystals arising via the vapor–liquid–solid (VLS) mechanism (Renard et al., 2009; Wagner and Ellis, 1964; Wang et al., 2006b), nanowire assembling and electrodes fabrication via photolithographic procedures to construct functional devices then follow (Patolsky et al., 2006).

The ultra-sensitivity of a SiNW-FET biosensor is demonstrated by its use in detecting biomolecules on the femtomolar level (Chen et al., 2011b; Cui et al., 2001). However, bio-analytes for molecular detection using SiNW-FETs are mostly large molecules with multiple charges, which yield a strong electric field to facilitate detection by FETs (Li et al., 2013a). Though the sensitivity of SiNW-FET biosensor is well recognized, its intrinsic limitation still presents a challenge for application to weakly charge, small molecules or extremely low concentration of large molecules, e.g. cancer markers. Accordingly, researchers are forced to consider different strategies to improve the sensitivity of SiNW-FET (Li et al., 2014).

There were many review articles on the applications of utilizing SiNW-FETs as sensors for detection of biological species with various attractive features including high sensitivity and direct electrical readout (Chen et al., 2011b; Patolsky and Lieber, 2005; Patolsky et al., 2007). However the conjugating method to link the organic bio-receptor with the inorganic transducer for various purposes and the fundamental factors affecting the device sensitivity are much less discussed. Therefore, the main feature of the present review will focus on the various methods for receptor immobilization and the latest development on sensitivity improvement of SiNW-FETs biosensors. We start with a brief description on the working principle of field-effect transistors, surface modification, and followed by detail discussions on the strategies of sensitivity improvement, that includes minimizing non-specific binding, structural design of the device, frequency-domain measurement (Zheng et al., 2010), sensing in the sub-threshold regime (Gao et al., 2010), and detecting of uncharged biomolecules (Chang et al., 2009).

## 2. Working principle and system setup

As the schematic illustration shown in Fig. 1A, a typical three-electrode SiNW-FET-based biosensor, includes source, drain, and gate electrodes. Source and drain electrodes function as the bridgeheads of the semiconductor channel (SiNWs) and allow the current flowing from source to drain, while the gate electrode is employed to modulate the channel conductance and to stabilize the signal by reducing electron density accumulated in the microfluidic channel. Selectivity is the other important characteristic for the biosensor. In the SiNW-FET system, the biological receptors were anchored on the surface of silicon nanowires to recognize target analytes through their highly specific binding affinity. When the target is bound by receptors, the surface potential undergoes changes and the channel conductance is modulated. The conductance changes are recorded and further processed by the electric measurement system. For example (Fig. 1B), when positively charged target molecules bind to the receptor immobilized on an n-type semiconductor channel, electron carriers are increased in the semiconductor channel and resulting in an enhanced conductance. On the other hand, when negatively charged target molecules are captured by the receptor, the electron carriers decrease and hence reduce the electrical conductance. Since immune-FETs, antibody modified FET sensors, are the most frequently used FET biosensors, the physiologically similar environment is prepared for biosensing by using phosphate buffered saline (1× PBS, 137 mM NaCl, 2.7 mM KCl, 10 mM $Na_2HPO_4$, 2 mM $KH_2PO_4$, pH 7.4 with NaOH). However, in high ionic solution the electric field of analyte is, at least partially, screened by the buffer solution, and accordingly, the signal is weakened. The screening effect is dependent on ionic strength, therefore to select a electrolytic buffer solution with an appropriate Debye–Hückel screening length ($\lambda_D$) to avoid jeopardizing of signal collection is necessary (Stern et al., 2007; Vacic et al., 2011; Zhang et al., 2008b).

## 3. Surface modification

As discussed above, SiNW-FET can serve as an ultrasensitive platform for biomolecule detection. Through strong affinity between the analyte and the receptor immobilized on silicon nanowire, SiNW-FET can selectively trap the target molecule and further convert the action of binding to the electrical signal. Therefore, how to effectively anchor the organic receptor on an inorganic device through chemical modification is an important issue for the fabrication of SiNW-FET biosensor. Silica ($SiO_x$ Lee and Su, 2009), auto-oxidized oxide layer of SiNWs) and silicon (SiH Nichols et al., 2005; Yam et al., 2004), surface of wet-etched SiNWs) are two major types of SiNW surface. Self-assembled