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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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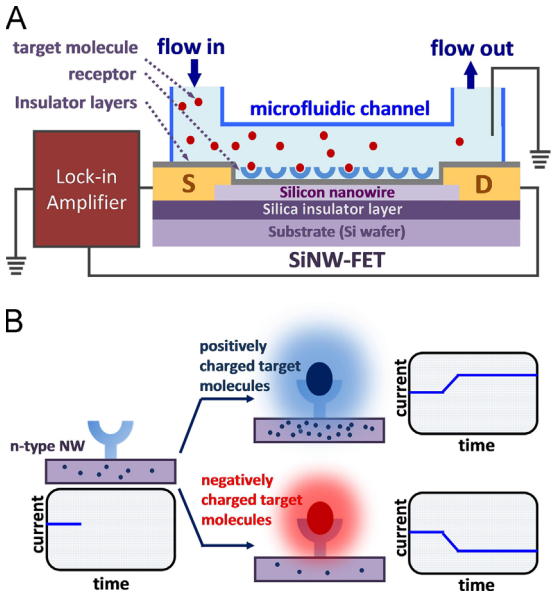


Fig. 1. Schematic illustrations of the working system and principle of the SiNW-FET biosensor. (A) A SiNW-FET is composed of a single SiNW (or a bunch of SiNWs), which is connected between a source (S) and drain (D) electrodes, laid on a Si wafer. The PDMS channel sitting on SiNW-FET device is utilized 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 ($1\times$ 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 (λ_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

monolayer (SAM) approach is ordered molecular assemblies formed by the spontaneous adsorption of an active molecular precursor onto a solid surface. Usually the precursor molecular species are dissolved in common solvents, however SAMs can be deposited by other techniques, such as vapor deposition, as well. SAMs with the silane based chemicals is the typical way to functional the silica surface of silicon nanowires. For example, several chemical processes have been developed to facilitate the surface modification of SiNW (Aswal et al., 2006; Herzer et al., 2010; Zhang et al., 2010), in which immobilization of the receptor on the silicon oxide layer is the most common strategy in view of the ease of chemical reaction and the insulated property that prevents the current leakage in the electrical measurement. In the following sections, cases of silanization on the SiNW-FET with various silane derivatives will be discussed.

3.1. Functionalization on silica surface

The most common method to functionalize the silica surface is through self-assembly of alkoxysilane-based linker, namely silanization. In this step, the hydroxyl groups on the SiNW surface attack and displace the alkoxy groups on a silane-based linker to form a covalent –Si–O–Si– bond. In general, the modification is performed either in the solution phase (Herzer et al., 2010) or in gas phase with evaporated chemical linkers (Li et al., 2013a; Zhang et al., 2010). Using oxygen plasmaor (Cui et al., 2001) UV/ozone (Uosaki et al., 2004) to clean the surface of SiNW is an essential step for attaining high quality silanization. The oxygen plasma not only removes organic contamination but also converts the entire surface to the silanol group (Aswal et al., 2006).

3-Aminopropyltrimethoxysilane (referred to APTMS) is the first silane utilized to functionalize nanowire with the silica surface. Cui et al., 2001 demonstrated that functionalized amine groups on the wire surface could be employed to chemical-link with the amine group of antibody (Yakovleva et al., 2002), proteins/enzyme (Aissaoui et al., 2013), NH_2-DNA (Crampton et al., 2005) by glutaraldehyde for the further bio-recognition (Table 1). In the subsequent studies, the APTMS-coated surface was utilizied to react with aldehydes, anhydrides, epoxides, and carboxylic acids for further functionalization. Other silane derivatives, such as 3-mercaptopropyltrimethoxysilane (MPTMS), can also be used to functionalize the wire surface. Thiol-functionalized surface can react with maleimide by Michael addition with specific functional groups, (e.g. carboxylic group, *N*-hydroxysuccinimide (Ebner et al., 2007)) and with dithiopyridine (Chen et al., 2011c) by disulfide bound exchange (Skinner et al., 2006) (Table 1). 3-Glycidoxypropyltrimethoxysilane is another silane having been demonstrated to react with amine-containing molecules (Table 1). Azide-functionalized surface can undergo the click chemistry with alkyne-contained molecules. In addition, 3-isocyanatopropyltriethoxysilane (Pandey et al., 1986) immobilized surface also can directly react covalently with primary amines (Table 1).

3.2. Functionalization on silicon surface

Heath's group (Bunimovich et al., 2006) reported the removal of the native oxide layer of silicon nanowire by hydrofluoric acid (HF), and the etched surface being a hydrogen-terminated silicon, can react with alkenes and alkynes to form the Si–C linked monolayer. The method was based on the observation of Cicero et al. (2000) and it still remains attractive due to its high efficiency. Either temperature or ultraviolet irradiation, is necessary for triggering the hydrosilylation (Buriak, 2002; Ciampi et al., 2010; Subramani et al., 2011). For example, the H-terminated surface reacts with *t*-butyl allycarbamate (Bunimovich et al., 2006) under irradiation at 254 nm. After deprotection of *t*-butyl ester, the amine group is exposed and is able to interact with biomolecules or undergo post-modification with organic compounds (Table 1) (Ciampi et al., 2010; Stern et al., 2007).

4. Sensitivity enhancement

4.1. Size effect on sensing sensitivity

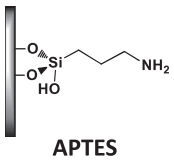
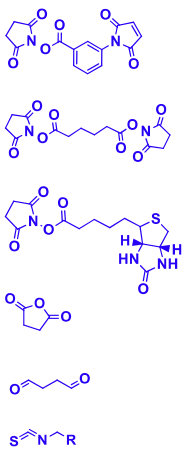
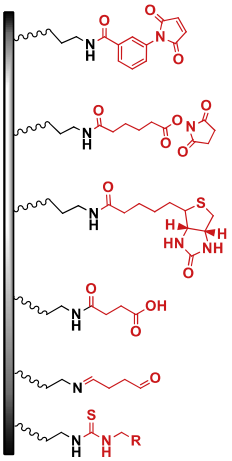
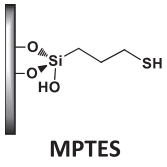
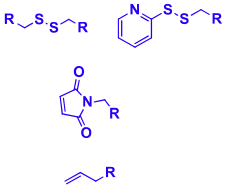
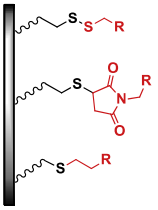
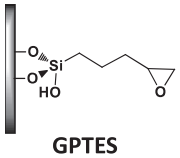
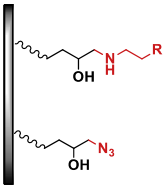
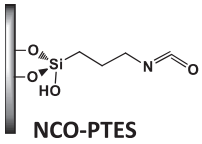
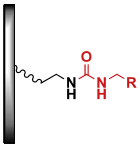
Elfstrom et al. (2007) have demonstrated the sensitivity of SiNW-FET is wire size-dependent. Their results showed that the nanowire-FET is more sensitive than the microwire-FET device. The surface-to-volume ratio of the wire in the nano-scale is relatively larger than the wire in micro-scale. Therefore, when thick wires are approached by charged particles, the area affected by the electric field exerted from the charged analyte is only located at the wire surface. Large interior wire areas are not affected and consequently the perturbation of conductance is less significant. As the wire diameter is decreased, the surface-to-volume ratio is increased drastically and the influence of the external electric field could reach the whole cross-section of the nanowires, which results in the induced conductance change inside the nanowire-FET significantly larger than the microwire-FETs.

4.2. Strategy for specific bio-conjugation on silicon nanowire

To achieve selective and ultra-sensitive detection of a target molecule, a specific receptor has to be immobilized on SiNW (Cui et al., 2001; Pui et al., 2011, 2009). As discussed previously, trialkoxysilane linkers are most frequently employed to introduce functional groups on SiNW surface for anchoring receptor molecules. However, the surface of the entire device including the nanowire (i.e. sensing area) and the rest of substrate is a homogeneous composition of silicon oxide after UV/ozone cleaning. As the chemical process conjugates trialkoxysilane-based linkers to silicon oxide surface without specificity, receptor molecules are immobilized on the chip in both sensing and non-sensing areas. Since the surface of the substrate is significantly larger than that of nanowire, all area modification results in a large proportion of target molecules being captured by the receptor on the surrounding substrate rather than at the sensing area. Consequently, the sensitivity is dramatically reduced. Simulation and experiment results also showed that by blocking the non-sensing region on the device could shorten the sensing time and increase the sensitivity, especially at lower target concentration (Buriak, 2002; Ciampi et al., 2010; Cicero et al., 2000). Therefore, selective modification of the linker on nanowire and reduction of the proportion on the non-sensing area are important for improving the sensitivity of SiNW biosensors. Several methods have been proposed to address this issue. Among them are photolithography (Stern et al., 2007), microcontact printing (Renault et al., 2002), electrostatic attraction (Naujoks and Stemmer, 2003), dip-pen nanolithography (Piner et al., 1999), and incomplete chemical etching (Masood et al., 2010; Zhang et al., 2008a). However, these methods either restrict to micrometer dimensions or require special instruments and skilled labors.

Localized Joule heating (Liu et al., 2013; Park et al., 2007; Yun et al., 2013) is the other “top-down”-based approach to limit the area of bio-conjugation. The method relies on a nanoscale Joule heating at a localized region of a nanowire. By applying an appropriate electrical bias across silicon nanowires, a localized high-temperature at the low doping region is created. This localized heating effect can be utilized to selectively evaporate the protecting polymer layer, e.g. poly(methylmethacrylate) (PMMA) (Park et al., 2007) or methoxylated poly(ethyleneglycol)

Table 1
Surface modification methodes on SiNWs.

Silane types	Reagents	Modified surface	Active functional groups	References
 APTES			  None   None	Chrisey et al. (1996) Puri et al. (2013) Kim et al. (2012) Liu and Han (2005) Wang and Jin (2004) Jin et al. (2012)
 MPTES			None None None	Skinner et al. (2006) Ebner et al. (2007) Lv et al. (2012)
 GPTES			None 	Liu et al. (2010) Henriksson et al. (2011), Sabitha et al. (2002)
 NCO-PTES			None	Pandey et al. (1986)

silane (mPEG-sil) (Liu et al., 2013), covering the region of the silicon nanowire. The exposed area becomes the only available surface for further modification (Fig. 2).

Li et al. (2013a) developed a method for selective surface modification (SSM) and allow the receptor to be conjugated only on the nanowires. The strategy involved in the preparation of SiNWs via the bottom-up manner and further treated with vaporized APTMS for surface modification of SiNWs prior to the photolithographic device fabrication. Consequently, the chemical linkers (APTMS) appear only on the nanowire surface. These SSM prepared SiNW-FETs exhibit ohmic contact and high transconductance, and such features have brought the SSM SiNW-FETs into an ultra-sensitive biosensor. The bindings of biotin/avidin and dopamine/phenylboronate served as successful demonstrations for SSM SiNW-FETs with faster response time, smaller sample requirements and significantly improved sensitivity up to two orders at a limited sample volume (5 μL) (Fig. 3).

4.3. Alignment of surface probes

The modification of silane-based linkers on silica surface has been reported to approach the level of self-assembly-monolayer (SAM) (Cui et al., 2001). However, linker molecules are randomly polarized and oriented (as shown in Fig. 4A). This result causes a problem for biosensing because an unaligned monolayer will dramatically reduce the collective charge polarization brought about by destructive interference. The detection becomes less sensitive.

For this reason, Chu et al. (2013) proposed a method to homogenize the orientation of the chemical linker by applying an external voltage (V_E) on a metal plate about 1 mm above the chip surface while grounding the back gate electrode (see Fig. 4B). In this process, 0.5 V electrical field was applied by an on-and-off cycle, and in each cycle containing electrical field on for 1 min and relaxation for 30 s. After aligning the linker for 30 cycles, the molecular conformation can be maintained for hours or longer. They further immobilized poly-15A ssDNAs on the chip, through the above modification and alignment procedures, for detection of DNA hybridization reactions with poly-15T ssDNAs. In comparison with the untreated device, the alignment process promotes the sensitivity of device by 10-fold (Fig. 4). In summary, this electric field alignment technique yielded parallel shift of $I-V_g$ curve at each stage of the modification, which is a signature of high quality surface modification on SiNW-FET sensors, with enhanced detection capability and reliability.

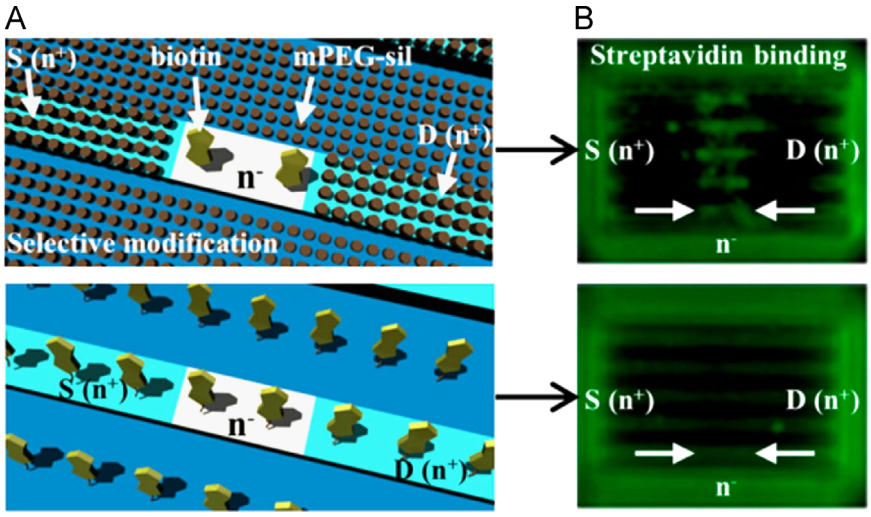


Fig. 2. (A) Schematic illustrations of selective and nonselective modification on the top-down based SiNW-FET. The up panel shows the selectively modified receptors (biotin) on the sensing area, which is prepared by self-assembled monolayer (SAM) of methoxy poly(ethyleneglycol)silane (mPEG-sil) on the silicon dioxide surface of SiNW-FET then localized Joule heating to expose sensing area for labeling biotin. The bottom panel shows the entire area of non-protected device is modified by biotin. (B) Fluorescent images of FITC-streptavidin binding on a selective (up panel) and non-selective modified device (bottom panel) (Liu et al., 2013).

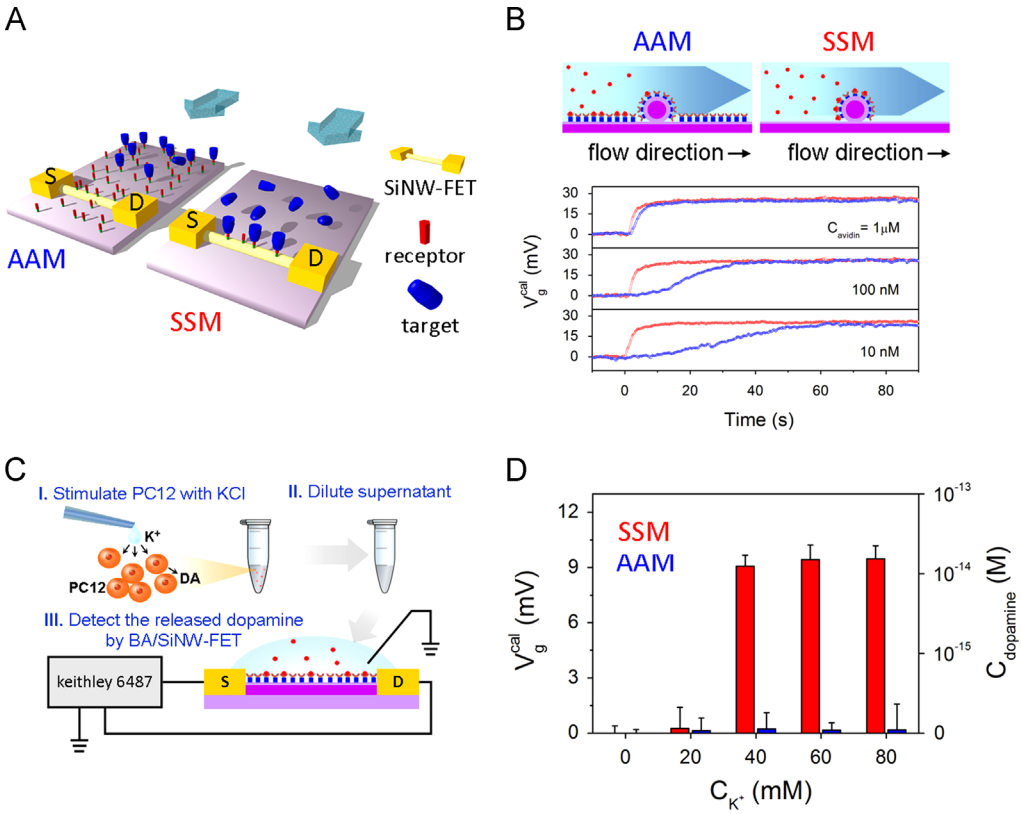


Fig. 3. (A) An illustration of biomolecular detection using the all-area-modified (AAM) or selective-surface-modified (SSM) SiNW-FET in a microfluidic system. (B) Real time recordings of avidin perfused onto the SSM biotin/SiNW-FET (red traces) and the AAM biotin/SiNW-FET (blue traces). (C) Illustration of the detection of dopamine released from PC12 cells by potassium stimulation. (D) Detection of dopamine, using SSM (red) and AAM (blue) BA/SiNW-FETs, in the sample collected from PC12 cells stimulated with various concentration of potassium (Li et al., 2013a).

4.4. *Strategy for small and/or uncharged molecule detection*

Although the SiNW-FET is believed to be one of the most sensitive and powerful devices for biological sensing, the detection is only feasible for analyte that carries charges. Note that the sensing principle of SiNW-FET is based on the variation of conductivity resulted from a charge perturbation on the surface of the nanowire, it is difficult for SiNW-FET to serve as a sensitive sensor for the weakly charged or uncharged analytes. To test the limitation of SiNW-FET, Cheng et al. studied the detection of 19-norandrostendione (19-NA), an uncharged molecule, using an engineered Δ^5-3-ketosteroid isomerase (KSI) (Chang et al., 2009; Sheu et al., 2008). As shown in Fig. 5A, the engineered KSI contains a long carbon chain molecule with a sulfonated reporter moiety, namely [5-(2-aminoethylamino)-1-naphthalenesulfonic acid], directly linked to the periphery of the steroid binding site

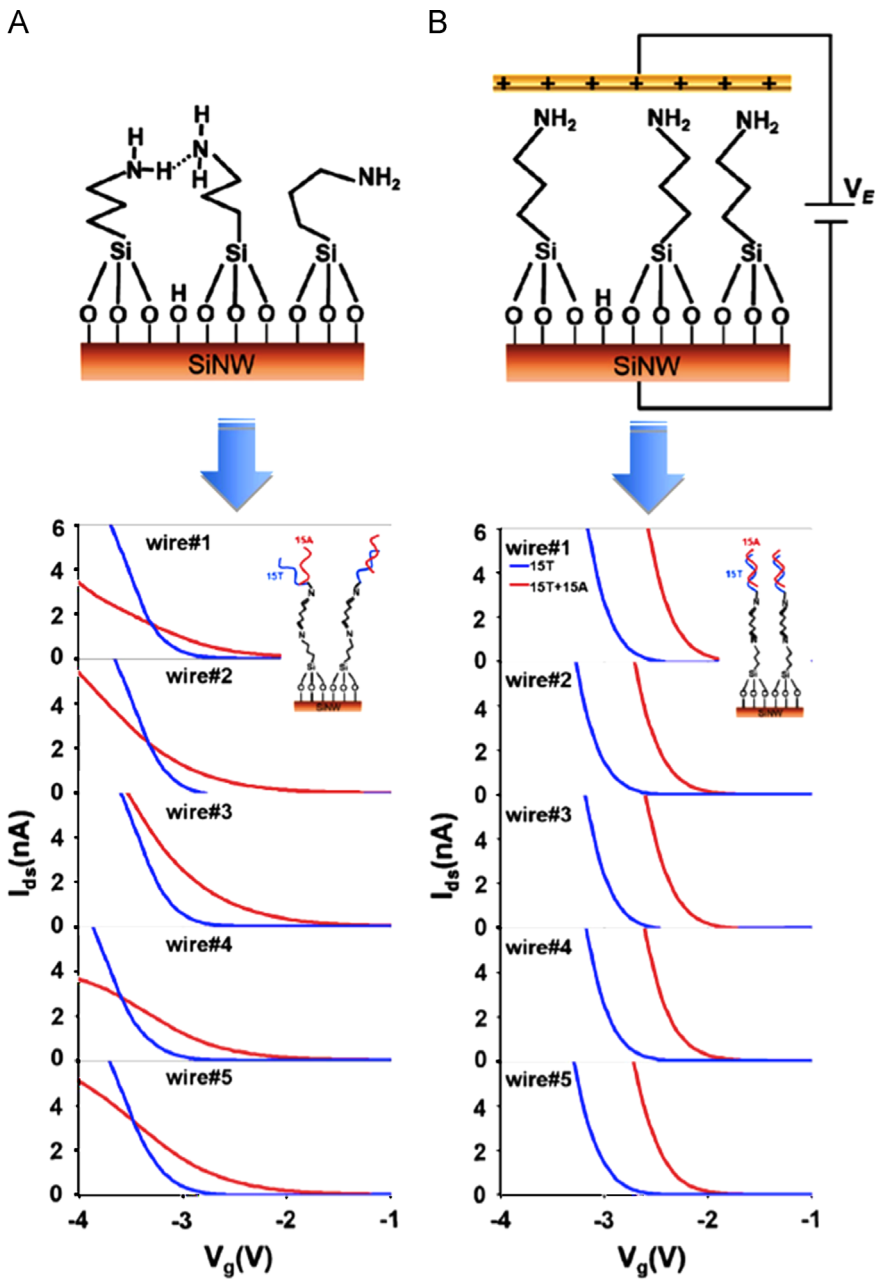


Fig. 4. Comparison of the effect of E-field alignment on the detection of DNA hybridization. The upper panels of (A) and (B) the possible orientation of APTES before and after alignment process. The bottom panels exhibit $I-V_g$ curves of five SiNWs without (A) or with (B) E-field alignment. Blue and red curves indicate $I-V_g$ curves before and after hybridization of 15T ssDNA with the immobilized probe, respectively (Chu et al., 2013).

with some part of the reporter molecule accommodated within (Chang et al., 2010). This engineered KSI, further immobilized on silicon nanowire, functions as the apparatus for the steroid recognition (Sheu et al., 2008). In the presence of steroid, the reporter can be expelled from the steroid binding site and is exposed to the surface of the nanowire. The negatively charged reporter moiety serves to change the surface potential of the nanowire, allowing for further quantitative assessment. As observed, no electrical field was created when steroid (a neutral analyte) bound to the wild-type KSI (Fig. 5B). With the reporter on SiNW-FET, an uncharged 19-NA can be detected with the sensitivity of femtomolar concentration (Fig. 5C).

Though the study has successfully demonstrated the service of SiNW-FET as an ultra-sensitive biosensor for uncharged analytes through the integration of protein engineering and chemical modification, a more general strategy is desirable for fulfilling the need of various targets. The concept of open sandwich immunoassay can be applied to the SiNW-FET biosensors. By combining the technique of phage display library screening, a single-chain variable fragment (scFv) can be possibly obtained for any target. The scFv is a fusion protein of variable light chain and heavy chain region of an antibody that possesses the recognition site for analyte. The scFv is easily massively produced by a common protein expression and purification protocol. For analytes of high molecular weights such as protein, DNA, virus, and even bacteria, the scFv can be directly used as the receptor, functioning as a regular antibody, for analyte recognition since the electrical signal induced by the target analyte is strong enough for SiNW-FET sensing. Whereas, for the detection of small molecules, the scFv will need to be dissected and further expressed into the

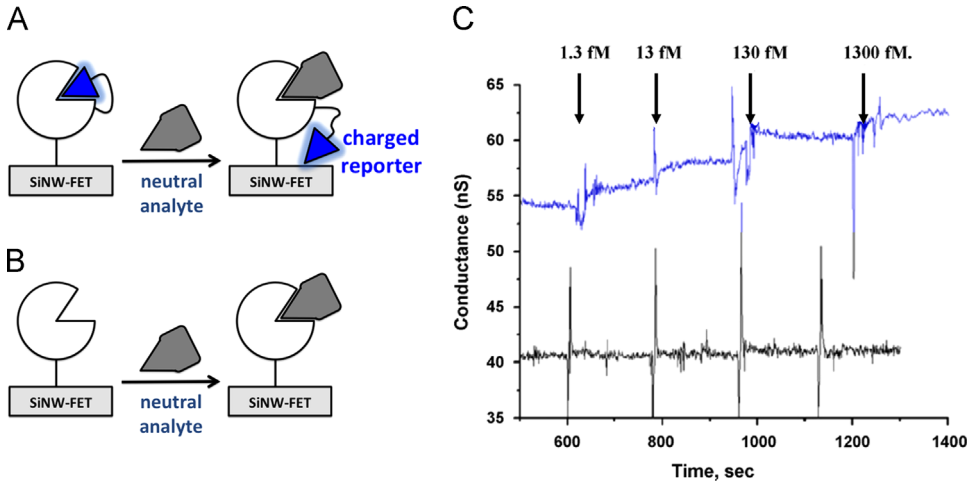


Fig. 5. A strategy on detection of an uncharged steroid, 19-NA. The detection of steroid by a SiNW-FET with (A) or without (B) the designed receptor. (C) Real-time recording the conductance response in the presence of 19-NA by a SiNW-FET with (upper) or without the designed receptors. Arrows indicate the point of addition of 19-NA to SiNW-FET at concentrations (1) 1.3 fM, (2) 13 fM, (3) 130 fM, and (4) 1300 fM (Chang et al., 2010).

variable heavy chain (V_H) and light chain (V_L) proteins. The intact recognition site will be formed only when the target analyte is present for inducing the formation of ternary complex of V_H-analyte-V_L. In the presence of an analyte, the FET signal can be greatly enhanced by one of the variable chain (e.g. V_H) that forms a ternary complex with the other (e.g. V_L) immobilized counter-part (Fig. 6) (Ueda et al., 1996).

4.5. Novel design of nano-structure

4.5.1. Suspended nanowire FET

Suspending nanowires above a substrate to form novel architectures is expected to improve both the sensing response time and the sensitivity of nanowire-FET (Lee et al., 2008). A suspended nanowire has size double that of a wire laid on the floor. Accordingly the number of receptors immobilized on the wire surface is increased. Moreover, the improvement also comes from the upper vertical region to reveal a higher local convection velocity around the nanowires, which replenishes the analyte faster and increases the diffusional fluxes of the analyte to the nanowire surface, consequently shortening the response time of sensing and increasing the sensitivity.

Several methods have been proposed to prepare suspended SiNWs in the past (Lee et al., 2008; San Paulo et al., 2007). For example, a "top-down"-based method (Lee et al., 2008) was to fabricate suspended silicon nanowire bridges via micromachining processes. The method was initiated by using deep reactive ion etching (DRIE) to following with anisotropic etch on a silicon substrate patented by photolithography. The height of the nanowire from the substrate can also be defined through this process. Owing to the differences of etching rates among the (1 1 1), the (1 0 0), and (1 1 0) planes, the anisotropic wet etchings with tetramethylammonium hydroxide (TMAH) and KOH provide silicon lines with triangular shaped cross sections. At the end, a narrow silicon column is released from the (1 1 1) bridge-structure, and the supporting pillar near the middle of the silicon column is completely etched.

4.5.2. Nanostructure on silicon nanowire

Due to limitation of lithography process, the top-down process for SiNW fabrication remains challenging in reducing wire size to 20 nm or below. However, as the sensitivity of SiNW-FET stems from the high surface-to-volume ratio (SVR) of the nanowire. Another feasible method to enlarge SVR of nanowires should be considered.

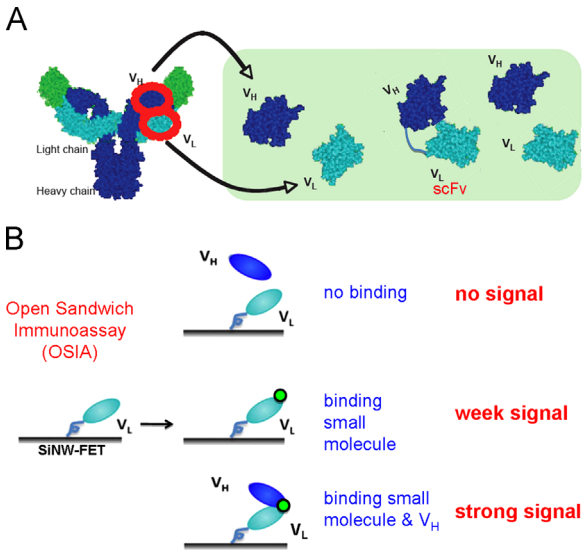


Fig. 6. A general strategy on detection of small molecule by open sandwich immunoassay technique. (A) Illustration of the structures of antibody, single-chain variable fragment (scFV), and opened variable fragment. (B) The application of the open sandwich immunoassay (OSIA) on a FET device. Note that, the sensing signal is largely enhanced by the counter-part fragment of scFv.

Seol et al. (2012) developed a localized nanoforest structure on a top-down fabricated silicon nanowire FET. They used localized Joule-heating method to remove PMMA on SiNW. Subsequently, 70 Å Au film was thermally deposited on the nanowires. With this thickness and thermal condition, gold film was directly annealed to form particles. The metal-assisted chemical etching (mac-etch) was then employed to construct the nanostructure from the original nanowire. The fabrication was completed after removing Au and PMMA by etchant. With this process, the nanoforest was formed only in the channel region without misalignment due to the self-aligned process of Joule-heating (Fig. 7A and B). Experimental results clearly showed that the modified SiNW-FET was endowed with improved sensitivity (Fig. 7C). Similar architecture has also been reported by selective growth of Au particle or ZnO

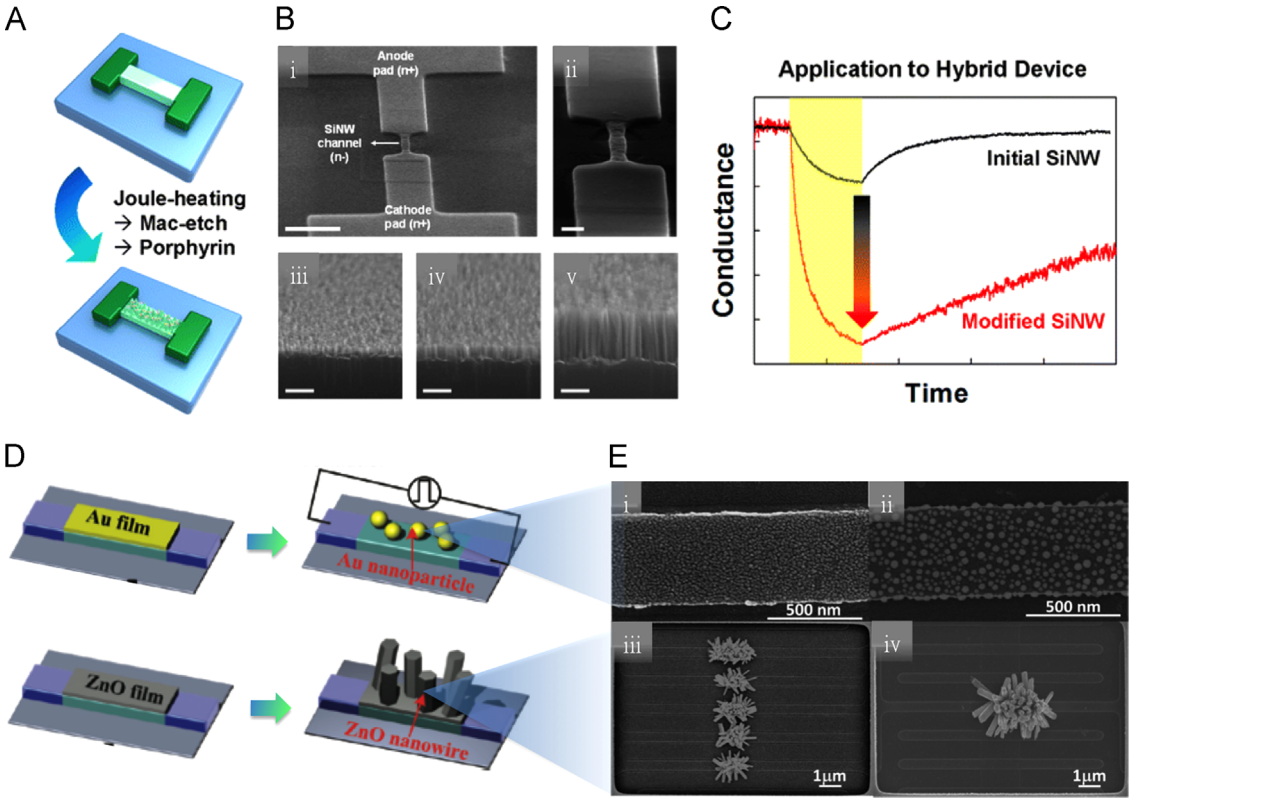


Fig. 7. (A) The illustration of procedure for fabricating the localized nanoforest-modified SiNW. (B) Bird's eye view SEM images of the nanoforest SiNW-FET device. (C) Real time recording of the response of UV induced conductance change on the porphyrin modified conventional SiNW-FET (black) and the SiNW-FET with sub-nanoforest structure (red). (D) The schematic fabrications of precisely formed AuNPs and grown ZnO NWs on the nano-FET device. (E) SEM images of the as-grown ultra thin Au film (i) and after the localized joule heating (ii). Typical SEM images of ZnO NWs selectively grown on multiple (i) and single nanowire (ii) devices (Chen et al., 2011a; Seol et al., 2012).

nano-rod on SiNW to increase the surface of the device (Fig. 7D and E) (Chen et al., 2011a).

4.5.3. *Multiple channels SiNW-FET*

Transconductance is defined as the ratio of the current change at the output port to the voltage change at the input port, which is the typical character utilized to adjudge the sensitivity of SiNW-FET. When the signal of weakly charged small molecules induced tiny current response is buried in the white noise, enhancement of the S/N ratio was attempted by several groups on building multiple nanowires SiNW-FETs to increase the transconductance. In addition, the surface of a SiNW (ex: $2\,\mu m \times \phi$ 20 nm) is particularly tiny to allow only 10^3–10^4 receptor molecules (i.e. bait proteins) to label on it. Small amounts of the binding sites are associated with signal uncertainty, which comes from the dynamic binding of targets and receptors. To overcome these two problems, the multiple nanowires SiNW-FET system was developed to increase the current and reduce the noise (Bunimovich et al., 2006; Fan et al., 2008; Tian et al., 2011).

Several multiple nanowires SiNW-FETs have been fabricated by either "bottom-up" (Lin et al., 2013) and "top-down" (Tian et al., 2011) approaches. For example, Li et al. used a contact printing method (Lin et al., 2013; Pregl et al., 2013) to align SiNWs on the substrate prior to the device fabrication. In their case, the as-fabricated FET typically contains 200–500 SiNWs. The transconductance of a multi-SiNW-FET is generally $>30{,}000$ nS as measured by back-gate voltage scanning in the ambient condition, that is hundreds times stronger than the single wire SiNW-FET.

In summing up the previous studies, it is evident that multi-SiNW-FETs provide less performance variations and better device stability in comparison with single-SiNW-FETs (Huang et al., 2012). Since the device with multi-SiNW-FETs accumulates and averages the signal output of individual SiNWs, it is less sensitive to the dopant fluctuations in SiNWs (Aissaoui et al., 2013) and environmental interference in electrical measurements. Also, multiple-SiNW-FETs offer higher driving current to improve the signal-to-noise ratio in bio-detections (Fig. 8) (Pregl et al., 2013; Regonda et al., 2013).

4.6. *Sensing in the sub-threshold regime*

Some fundamental considerations of the devices can be utilized to optimize the sensitivity of SiNW-FET. For example, a smaller wire size and a small thickness of silica layer on the SiNWs allow the electric field to penetrate through the entire cross section of nanowires. The other well-known factor affect the sensitivity of the SiNW-FET is the doping concentration. Generally, the SiNW-FET with lower doping ratio (10^{17} atom/cm^3) reveals a >3-fold sensitivity increase than the device with the heavy dopant (10^{19} atom/cm^3), due to reduction of the screening effect by electron carriers/holes in the silicon nanowires (Li et al., 2011). However, the optimized doping ratio is not easy to control. Gao et al. (2010) found an easy way to significantly increase the sensitivity of SiNW-FET by reducing the screening effect for the silicon nanowires. They noted that the sensitivity of the SiNW-FET biosensor could be exponentially enhanced when working in the sub-threshold regime, which allowed the gating effect from molecules bound onto the surface more efficiently. This principle was exemplified in the detection of prostatic specific antigen (PSA), a well-known protein marker for prostate cancer, by anti-PSA antibody immobilized SiNW-FET. The typical detection limit of

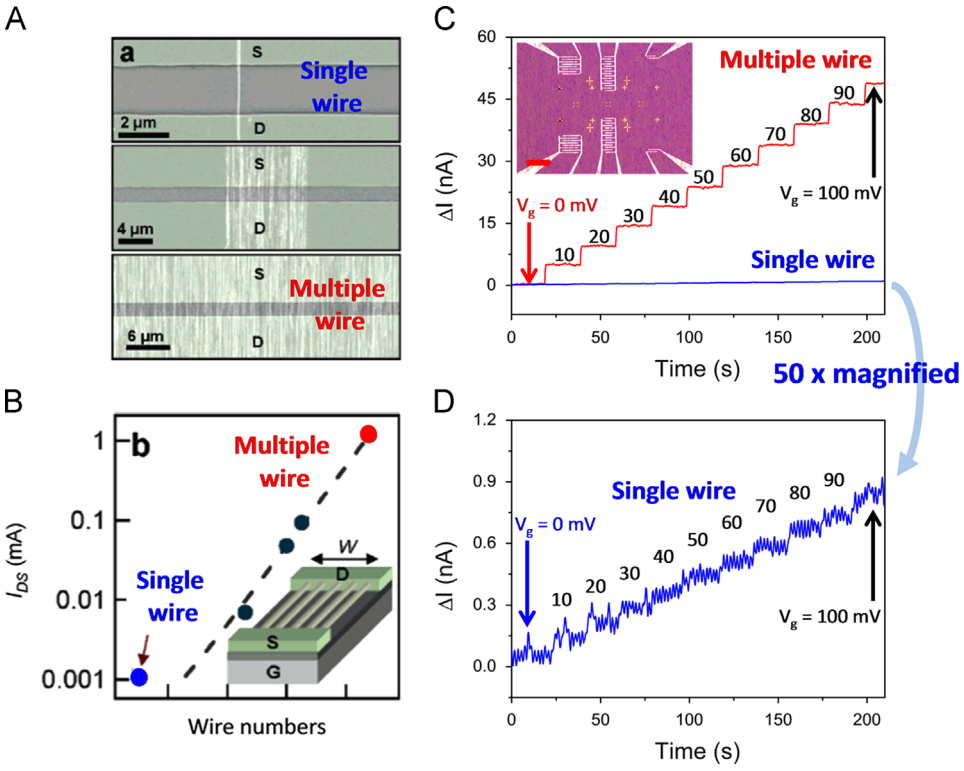


Fig. 8. (A) and (B) shown the comparison of the sensitivities of a multiple-parallel-connected (MPC) SiNW-FET and a conventional SiNW-FET with a conducting channel consisting of only a single SiNW (Fan et al., 2008; Pregl et al., 2013). (C) The ΔI_{sd} vs. elapse time plots were measured as a function of the applied (solution) gate voltage (V_g) through an Ag/AgCl reference electrode from 0 to 100 mV with an increasing rate of 10 mV/step. Relative to the measurement by conventional SiNW-FET, a significant improvement (more than 100-fold) in the S/N ratio of the signals measured by MPC SiNW-FET is clearly observed. Inset of (C) is the optical image of multiple-parallel-connected (MPC) SiNW-FET. (C) and (D) shown the signal to noise ratio could be significantly improved in the multiple-parallel-connected (MPC) SiNW-FET system (Li et al., 2013b).

Table 2
Advantages of various sensitivity enhancing strategies.

Strategies	Advantages	References
Reduce wire size	Increased the signal response; sensitivity improved	Elfstrom et al. (2007)
Reduce oxide thickness	Increased the signal response; sensitivity improved	Bunimovich et al. (2006)
Selective receptor modification	Reduce the binding time; sensitivity improved	Li et al. (2013a), Liu et al. (2013)
Alignment of the probe	Repeativity improved	Chu et al. (2013)
With repoter enhancers	Enhance the signals	Chang et al. (2009), Sheu et al. (2008)
Suspended structure	Reduce the binding time	Lee et al. (2008), San Paulo et al. (2007)
Subnanostructure on wire	Enhance the signals; increase the binding site	Chen et al. (2011a), Seol et al. (2012)
Multiple wires net work	Enhance the signals; increase the binding site	Li et al. (2013a, 2013b), Wang et al. (2006a)
Detect in the sub-threshold regime	Increase the signal response	Gao et al. (2010)

PSA by a standard SiNW-FET sensor at the linear regime (V_g=0) is around 15 pM, while the detection is improved to approach 1.5 fM at the sub-threshold regime (V_g=0.45 V). The sensitivity of protein detection can be enhanced by three orders in concentration by operating the SiNW-FET sensor at the sub-threshold regime instead of the conventional linear regime. Thus it was concluded that the most sensitive SiNW-FET biosensor should rely on the gating effect of target molecules throughout the whole cross section of nanowires. For this purpose, a longer carrier screening length is required, and a lower dopant SiNW or operating the SiNW-FET sensor working in the sub-threshold regime by solution gate is strongly recommended.

5. Summary

SiNW-FET, a highly selective and sensitive biosensor, can be utilized for real time and label-free detection of biological species in buffer solution. Its applications range from protein to protein interaction, DNA/RNA/PNA hybridization, virus detection, electrical response of neuron cells, to clinical diagnosis. In this mini-review, we have described the working principles, various immobilization methods, the strategies to increase the sensitivity of SiNW-FET including subjects of (I) minimize the wire size, (II) specific bio-conjugation on silicon nanowire, (III) alignment of surface probes, (IV) strategy for small and/or uncharged molecule detection, (V) novel design of nano-structure such as the suspended SiNW, sub-nanostructure on wire surface, and multiple nanowires, and (VI) sensing in the sub-threshold regime (Table 2). Using these strategies, the stability and the resolution of signal response of SiNW-FET can be significantly improved. SiNW-FETs were also demonstrated to detect target analytes with large size, including proteins, DNAs, and viruses, as well as small molecules with or without charge. Nevertheless, there are some challenges still remained. For example, whole blood samples cause a strong background due to the high ionic strength and non-specific

binding on the device. It implies the need for current biosensing a prior desalting process to increase the Debye–Hückel screening length (λ_D) and to avoid serum fouling on the device. In addition, the supports for fabrication of the new design of novel devices and the signal acquisition system for high-throughput multiplexed sensing are essential for clinical diagnosis and further industrial applications. Although some challenges still needs to be overcome, we believe that SiNW-FET biosensor will play a significant role in biological analysis and cellular investigations in near future.

Acknowledgements

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References

Aissaoui, N., Landoulsi, J., Bergaoui, L., Boujday, S., Lambert, J.F., 2013. Enzyme Microb. Technol. 52 (6–7), 336–343.
Allsop, T., Neal, R., Dvorak, M., Kalli, K., Rozhin, A., Webb, D.J., 2013. Opt. Express 21 (16), 18765–18776.
Arlett, J.L., Myers, E.B., Roukes, M.L., 2011. Nat. Nanotechnol. 6 (4), 203–215.
Aswal, D.K., Lenfant, S., Guerin, D., Yakhmi, J.V., Vuillaume, D., 2006. Anal. Chim. Acta 568 (1–2), 84–108.
Britto, P.J., Santhanam, K.S.V., Ajayan, P.M., 1996. Biosens. Bioelectron. 41 (1), 121–125.
Bunimovich, Y.L., Shin, Y.S., Yeo, W.S., Amori, M., Kwong, G., Heath, J.R., 2006. J. Am. Chem. Soc. 128 (50), 16323–16331.
Buriak, J.M., 2002. Chem. Rev. 102 (5), 1271–1308.
Chang, K.S., Chen, C.C., Sheu, J.T., Li, Y.-K., 2009. Sens. Actuators, B 138 (1), 148–153.
Chang, K.S., Luo, L., Chang, C.W., Huang, Y.C., Cheng, C.Y., Hung, C.S., Diau, E.W., Li, Y.K., 2010. J. Phys. Chem. B 114 (12), 4327–4334.
Chen, C.C., Lin, Y.S., Sang, C.H., Sheu, J.T., 2011a. Nano Lett. 11, 4736–4741.
Chen, K.I., Li, B.R., Chen, Y.T., 2011b. Nano Today 6 (2), 131–154.
Chen, Q., Tang, W., Wang, D.Z., Wu, X.J., Li, N., Liu, F., 2010. Biosens. Bioelectron. 26 (2), 575–579.
Chen, X., Chen, H., Tripisciano, C., Jedrzejewska, A., Rummeli, M.H., Klingeler, R., Kalenczuk, R.J., Chu, P.K., Borowiak-Palen, E., 2011c. Chemistry 17 (16), 4454–4459.
Chen, Z.B., Chen, L., Ma, H., Zhou, T., Li, X.X., 2013. Biosens. Bioelectron. 48, 108–112.
Chiang, P.-L., Chou, T.-C., Wu, T.-H., Li, C.-C., Liao, C.-D., Lin, J.-Y., Tsai, M.-H., Tsai, C.-C., Sun, C.-J., Wang, C.-H., Fang, J.-M., Chen, Y.-T., 2012. Chem.: Asian J. 7 (9), 2073–2079.
Chrisey, L.A., Lee, G.U., O'Ferrall, C.E., 1996. Nucleic Acids Res. 24 (15), 3031–3039.
Chu, C.J., Yeh, C.S., Liao, C.K., Tsai, L.C., Huang, C.M., Lin, H.Y., Shyue, J.J., Chen, Y.T., Chen, C.D., 2013. Nano Lett. 13 (6), 2564–2569.
Ciampi, S., Harper, J.B., Gooding, J.J., 2010. Chem. Soc. Rev. 39 (6), 2158–2183.
Cicero, R.L., Linford, M.R., Chidsey, C.E.D., 2000. Langmuir: ACS J. Surf. Colloids 16 (13), 5688–5695.
Clark Jr., L.C., Lyons, C., 1962. Ann. N.Y. Acad. Sci. 102, 29–45.
Crampton, N., Bonass, W.A., Kirkham, J., Thomson, N.H., 2005. Langmuir: ACS J. Surf. Colloids 21 (17), 7884–7891.
Cui, Y., Wei, Q., Park, H., Lieber, C.M., 2001. Science 293 (5533), 1289–1292.
Deng, L., Norberg, O., Uppalapati, S., Yan, M., Ramstrom, O., 2011. Org. Biomol. Chem. 9 (9), 3188–3198.
Ebner, A., Wildling, L., Kamruzzahan, A.S., Rankl, C., Wruss, J., Hahn, C.D., Holzl, M., Zhu, R., Kienberger, F., Blaas, D., Hinterdorfer, P., Gruber, H.J., 2007. Bioconjugate Chem. 18 (4), 1176–1184.
Elfstrom, N., Juhasz, R., Sychugov, I., Engfeldt, T., Karlstrom, A.E., Linnros, J., 2007. Nano Lett. 7 (9), 2608–2612.
Fan, Z., Ho, J.C., Jacobson, Z.A., Yerushalmi, R., Alley, R.L., Razavi, H., Javey, A., 2008. Nano Lett. 8 (1), 20–25.
Farre, M., Barcelo, D., 2003. TrAC, Trends Anal. Chem 22 (5), 299.
Gao, X.P., Zheng, G., Lieber, C.M., 2010. Nano Lett. 10 (2), 547–552.
Garcia-Martinez, G., Bustabad, E.A., Perrot, H., Gabrielli, C., Bucur, B., Lazerges, M., Rose, D., Rodriguez-Pardo, L., Farina, J., Compere, C., Vives, A.A., 2011. Sensors 11 (8), 7656–7664.
Haes, A.J., Van Duyne, R.P., 2002. J. Am. Chem. Soc. 124 (35), 10596–10604.
Hahm, J., Lieber, C.M., 2004. Nano Lett. 4 (1), 51–54.
Henriksson, A., Friedbacher, G., Hoffmann, H., 2011. Langmuir: ACS J. Surf. Colloids 27 (12), 7345–7348.
Herzer, N., Hoeppener, S., Schubert, U.S., 2010. Chem. Commun. 46 (31), 5634–5652.
Huang, P.C., Chen, L.A., Chen, C.C., Sheu, J.T., 2012. Microelectron. Eng. 91 (0), 54–58.
Jin, L., Fang, Y., Hu, P., Zhai, Y., Wang, E., Dong, S., 2012. Chem. Commun. 48 (15), 2101–2103.
Kim, S., Baek, D., Kim, J.-Y., Choi, S.-J., Seol, M.-L., Choi, Y.-K., 2012. Appl. Phys. Lett. 101 (7), 073703.
Kumar, J., D'Souza, S.F., 2011. Biosens. Bioelectron. 26 (11), 4289–4293.
Lee, K.N., Jung, S.W., Shin, K.S., Kim, W.H., Lee, M.H., Seong, W.K., 2008. Small 4 (5), 642–648.
Lee, W., Su, P., 2009. Nanotechnology 20 (6), 065202.
Li, B.R., Chen, C.C., Kumar, U.R., Chen, Y.T., 2014. Analyst 139 (7), 1589–1608.
Li, B.R., Chen, C.W., Yang, W.L., Lin, T.Y., Pan, C.Y., Chen, Y.T., 2013a. Biosens. Bioelectron. 45, 252–259.
Li, B.R., Hsieh, Y.J., Chen, Y.X., Chung, Y.T., Pan, C.Y., Chen, Y.T., 2013b. J. Am. Chem. Soc. 135 (43), 16034–16037.
Li, J., Zhang, Y., To, S., You, L., Sun, Y., 2011. ACS Nano 5 (8), 6661–6668.
Lin, M.C., Chu, C.J., Tsai, L.C., Lin, H.Y., Wu, C.S., Wu, Y.P., Wu, Y.N., Shieh, D.B., Su, Y. W., Chen, C.D., 2007. Nano Lett. 7 (12), 3656–3661.
Lin, T.W., Hsieh, P.J., Lin, C.L., Fang, Y.Y., Yang, J.X., Tsai, C.C., Chiang, P.L., Pan, C.Y., Chen, Y.T., 2010. Proc. Nat. Acad. Sci. U.S.A. 107 (3), 1047–1052.
Lin, T.Y., Li, B.R., Tsai, S.T., Chen, C.W., Chen, C.H., Chen, Y.T., Pan, C.Y., 2013. Lab Chip 13 (4), 676–684.
Liu, H.H., Lin, T.H., Sheu, J.-T., 2013. ACS Appl. Mater. Interfaces 5 (20), 10048–10053.
Liu, S., Han, M., 2005. Adv. Funct. Mater. 15 (6), 961–967.
Liu, Y.-C.C., Rieben, N., Iversen, L., Sørensen, B.S., Park, J., Nygård, J., Martinez, K.L., 2010. Nanotechnology 21 (24), 245105.
Lv, Y., Lin, Z., Svec, F., 2012. Analyst 137 (18), 4114–4118.
Malmqvist, M., 1993. Nature 361 (6408), 186–187.
Masood, M.N., Chen, S., Carlen, E.T., van den Berg, A., 2010. ACS Appl. Mater. Interfaces 2 (12), 3422–3428.
Naujoks, N., Stemmer, A., 2003. Microelectron. Eng. 67–68, 736–741.
Nichols, B.M., Butler, J.E., Russell Jr., J.N., Hamers, R.J., 2005. J. Phys. Chem. B 109 (44), 20938–20947.
Norouzi, P., Ganjali, H., Larijani, B., Ganjali, M.R., Faridbod, F., Zamani, H.A., 2011. Int. J. Electrochem. Sci. 6 (11), 5189–5199.
Ortiz, M., Fragoso, A., O'Sullivan, C.K., 2011. Org. Biomol. Chem. 9 (13), 4770–4773.
Pandey, R.N., Davis, L.E., Anderson, B., Hollenberg, P.F., 1986. J. Immunol. Methods 94 (1–2), 237–246.
Park, I., Li, Z., Pisano, A.P., Williams, R.S., 2007. Nano Lett. 7 (10), 3106–3111.
Patolsky, F., Lieber, C.M., 2005. Mater. Today 8 (5).
Patolsky, F., Timko, B.P., Zheng, G.F., Lieber, C.M., 2007. MRS Bull. 32 (2), 142–149.
Patolsky, F., Zheng, G.F., Hayden, O., Lakadamyali, M., Zhuang, X.W., Lieber, C.M., 2004. Proc. Nat. Acad. Sci. U.S.A. 101 (39), 14017–14022.
Patolsky, F., Zheng, G.F., Lieber, C.M., 2006. Nat. Protoc. 1 (4), 1711–1724.
Piner, R.D., Zhu, J., Xu, F., Hong, S.H., Mirkin, C.A., 1999. Science 283 (5402), 661–663.
Pregl, S., Weber, W., Nozaki, D., Kunstmann, J., Baraban, L., Opitz, J., Mikolajick, T., Cuniberti, G., 2013. Nano Res 6 (6), 381–388.
Pui, T.S., Agarwal, A., Ye, F., Huang, Y.X., Chen, P., 2011. Biosens. Bioelectron. 26 (5), 2746–2750.
Pui, T.S., Agarwal, A., Ye, F., Ton, Z.Q., Huang, Y.X., Chen, P., 2009. Nanoscale 1 (1), 159–163.
Puri, N., Sharma, V., Tanwar, V.K., Singh, N., Biradar, A.M., 2013. Prog. Biomater. 2 (1), 1–7.
Regonda, S., Tian, R., Gao, J., Greene, S., Ding, J., Hu, W., 2013. Biosens. Bioelectron. 45, 245–251.
Renard, V.T., Jublot, M., Gergaud, P., Cherns, P., Rouchon, D., Chabli, A., Jousseaume, V., 2009. Nat. Nanotechnol 4 (10), 654–657.
Renault, J.P., Bernard, A., Juncker, D., Michel, B., Bosshard, H.R., Delamarche, E., 2002. Angew. Chem. Int. Ed. 41 (13), 2320–2323.
Rodriguez, M.C., Kawde, A.N., Wang, J., 2005. Chem. Commun. 34, 4267–4269.
Rodriguez-Mozaz, S., de Alda, M.J.L., Barcelo, D., 2006. Anal. Bioanal. Chem. 386 (4), 1025.
Sabitha, G., Satheesh Babu, R., Shashi Kumar Reddy, M., Yadav, J., 2002. Synthesis 2002 (15), 2254–2258.
San Paulo, A., Arellano, N., Plaza, J.A., He, R.R., Carraro, C., Maboudian, R., Howe, R.T., Bokor, J., Yang, P.D., 2007. Nano Lett. 7 (4), 1100–1104.
Seol, M.L., Ahn, J.H., Choi, J.M., Choi, S.J., Choi, Y.K., 2012. Nano Lett. 12 (11), 5603–5608.
Sheu, J.T., Chen, C.C., Chang, K.S., Li, Y.K., 2008. Biosens. Bioelectron. 23 (12), 1883–1886.
Skinner, K., Dwyer, C., Washburn, S., 2006. Nano Lett. 6 (12), 2758–2762.
Stern, E., Klemic, J.F., Routenberg, D.A., Wyrembak, P.N., Turner-Evans, D.B., Hamilton, A.D., LaVan, D.A., Fahmy, T.M., Reed, M.A., 2007. Nature 445 (7127), 519–522.
Subramani, C., Cengiz, N., Saha, K., Gevrek, T.N., Yu, X., Jeong, Y., Bajaj, A., Sanyal, A., Rotello, V.M., 2011. Adv. Mater. 23 (28), 3165–3169.
Tian, R., Regonda, S., Gao, J., Liu, Y., Hu, W., 2011. Lab Chip 11 (11), 1952–1961.
Ueda, H., Tsumoto, K., Kubota, K., Suzuki, E., Nagamune, T., Nishimura, H., Schueler, P.A., Winter, G., Kumagai, I., Mahoney, W.C., 1996. Nat. Biotechnol 14 (13), 1714–1718.
Uosaki, K., Quayum, M.E., Nihonyanagi, S., Kondo, T., 2004. Langmuir: ACS J. Surf. Colloids 20 (4), 1207–1212.
Vacic, A., Criscione, J.M., Rajan, N.K., Stern, E., Fahmy, T.M., Reed, M.A., 2011. J. Am. Chem. Soc. 133 (35), 13886–13889.
Viswanathan, S., Radecka, H., Radecki, J., 2009. Monatsh. Chem. 140 (8), 891.
Wagner, R.S., Ellis, W.C., 1964. Appl. Phys. Lett. 4 (5), 89–90.
Wang, C.-W., Pan, C.-Y., Wu, H.-C., Shih, P.-Y., Tsai, C.-C., Liao, K.-T., Lu, L.-L., Hsieh, W.-H., Chen, C.-D., Chen, Y.-T., 2007. Small 3 (8), 1350–1355.
Wang, D., Sheriff, B.A., Heath, J.R., 2006a. Nano Lett. 6 (6), 1096–1100.

Wang, R., Du, L.P., Zhang, C.L., Man, Z.S., Wang, Y.J., Wei, S.B., Min, C.J., Zhu, S.W., Yuan, X.C., 2013. Opt. Lett. 38 (22), 4770–4773.
Wang, Y., Schmidt, V., Senz, S., Gosele, U., 2006b. Nat. Nanotechnol 1 (3), 186–189.
Wang, Y., Xu, H., Zhang, J.M., Li, G., 2008. Sensors 8 (4), 2043.
Wang, Z.H., Jin, G., 2004. J. Immunol. Methods 285 (2), 237–243.
Yakovleva, J., Davidsson, R., Lobanova, A., Bengtsson, M., Eremin, S., Laurell, T., Emneus, J., 2002. Anal. Chem. 74 (13), 2994–3004.
Yam, C.M., Lopez-Romero, J.M., Gu, J., Cai, C., 2004. Chem. Commun. 21, 2510–2511.
Yun, J., Jin, C.Y., Ahn, J.H., Jeon, S., Park, I., 2013. Nanoscale 5 (15), 6851–6856.
Zhang, F., Sautter, K., Larsen, A.M., Findley, D.A., Davis, R.C., Samha, H., Linford, M.R., 2010. Langmuir: ACS J. Surf. Colloids 26 (18), 14648–14654.
Zhang, G.J., Chua, J.H., Chee, R.E., Agarwal, A., Wong, S.M., 2009. Biosens. Bioelectron. 24 (8), 2504–2508.
Zhang, G.J., Chua, J.H., Chee, R.E., Agarwal, A., Wong, S.M., Buddharaju, K.D., Balasubramanian, N., 2008a. Biosens. Bioelectron. 23 (11), 1701–1707.
Zhang, G.J., Zhang, G., Chua, J.H., Chee, R.E., Wong, E.H., Agarwal, A., Buddharaju, K.D., Singh, N., Gao, Z., Balasubramanian, N., 2008b. Nano Lett. 8 (4), 1066–1070.
Zheng, G., Gao, X.P., Lieber, C.M., 2010. Nano Lett. 10 (8), 3179–3183.
Zheng, G.F., Lu, E., Jin, S., Lieber, C.M., 2004. Adv. Mater. 16 (21), 1890–1893.
Zheng, G.F., Patolsky, F., Cui, Y., Wang, W.U., Lieber, C.M., 2005. Nat. Biotechnol 23 (10), 1294–1301.