Chapter 10
Nanowire Field-Effect Transistor Sensors

Abstract Sensitive and quantitative analysis of proteins and other biochemical species are central to disease diagnosis, drug screening and proteomic studies. Research advances exploiting SiNWs configured as FETs for biomolecule analysis have emerged as one of the most promising and powerful platforms for label-free, real-time, and sensitive electrical detection of proteins as well as many other biological species. In this chapter, we first briefly introduce the fundamental principle for semiconductor NW-FET sensors. Representative examples of semiconductor NW sensors are then summarized for sensitive chemical and biomolecule detection, including proteins, nucleic acids, viruses and small molecules. In addition, this chapter discusses several electrical and surface functionalization methods for enhancing the sensitivity of semiconductor NW sensors.

10.1 Introduction

Fundamental biomedical research demands novel biosensors and assays that can fulfill the requirements of ultra-sensitivity and high-throughput [1, 2]. Many semiconducting nanomaterials, such as NWs, carbon nanotubes and graphene have been studied for the electronic sensing in an effort to address these needs. Among them, SiNWs possess unique structural and chemical characteristics, including diameters similar to proteins, high surface-to-volume ratios, chemically well-defined and tailorable silicon oxide surfaces, which have enabled them to be configured as high-performance FETs for label-free, real-time, sensitive detection of proteins and other biomolecules [3–5].

The electrical detection of biomolecules using a NW-FET can be understood as follows. The surface of a NW-FET is functionalized with biomolecule receptors, such as monoclonal antibodies or single-strand DNA (ssDNA) probes, which can selectively bind to biomolecule targets in solution. The binding of charged biomolecules, (the sign and number of charges depend on the isoelectric point of the biomolecules and the solution pH), leads to a variation of charge or electric potential at the NW surface, in a way similar to applying an external potential to gate electrode

in a conventional FET device. The charge carrier densities of the NW-FET is thus tuned and leads to an electrical conductivity change associated with the biomolecular binding events in real time. Since the NW diameters can be similar to biomolecules such as proteins and nucleic acids, these binding events can be sensitively detected by the NW-FETs. Furthermore, incorporation of a number of NW-FET elements in a single sensor chip where the NWs are functionalized with different surface receptors allows for multiplexed electrical detection in the same assay, enabling a unique and powerful platform for chemical/biological recognition [6].

In this chapter, we first briefly introduce the fundamental principles of the NW-FET sensor. Then, representative examples in which FET sensors are applied to detect chemical and biomolecule targets, including proteins, nucleic acids, viruses, and small molecules, are summarized. Furthermore, several methods for improving the sensitivity and/or capabilities of NW-FET sensors, including the use of branched NWs to enhance the capture efficiency of molecular analytes, operation of the FET in the subthreshold regime, increasing the analyte concentration by electrokinetic effects, and detection in physiological fluids, are briefly illustrated.

10.2   Fundamental Principles of Field-Effect Transistor Sensors

As previously discussed in Chap. 5, FETs are among the fundamental building blocks of today's high–density integrated circuits. In a standard planar metal-oxide semiconductor FET (Fig. 10.1a), the semiconductor substrate is connected to the gate (G), the source (S) and the drain (D) electrodes. If no gate voltage is applied (the "Off" state), the FET is equivalent to two back-to-back p–n junctions with almost no current flows. In the "On" state, when the gate bias exceeds a threshold voltage, carriers (e.g., holes for p–Si and electrons for n–Si) are induced at the semiconductor–oxide interface, the potential barrier of the channel drops, resulting in a significant current flow. Therefore, the conductance of the semiconductor channel between the source and drain regions can be switched on and off by the potential at the gate electrode.

The use of planar FETs for ion–selective sensors was introduced several decades ago [7], while their opportunities as chemical and biological sensors have further been advanced in new and significant ways using NWs. Similar to planar FET, the conductance of a NW-FETs can be controlled by variations in the charge density or electric potential in the channel region. This response makes NW-FETs ideal candidates for chemical and biological sensing, as the change in electric field due to binding of a charged molecule to the NW surface, which is analogous to applying a voltage via a gate electrode, can readily change the device conductance. For example, a p-type SiNW functionalized with surface receptors that can specifically capture chemical/biomolecule targets will exhibit an increase in conductance when negatively charged molecules bind to the receptors. This increase in conductance is
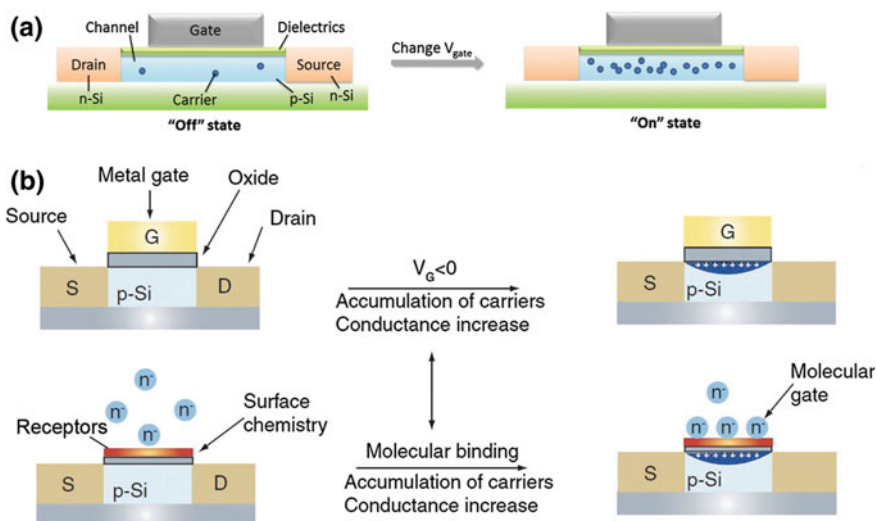
Fig. 10.1 **a** A typical planar FET. The semiconductor substrate (e.g., *p*–Si) is connected to gate (*G*), source (*S*) and drain (*D*) electrodes, and can be switches between the "off" and "on" states by applying the gate voltage. **b** Schematic comparison of (*top*) a standard FET device and (*bottom*) a SiNW-FET sensor. The NW surface is functionalized with a receptor layer to recognize target biomolecules in a solution, which are charged and provide a molecular gating effect on SiNWs. Reproduced from [76]. Copyright 2006 Future Medicine Ltd. (color figure online)

similar to applying a negative gate voltage and results from accumulation of charge carriers (holes) in the *p*-type FET (Fig. 10.1b). Conversely, binding positively charged molecules will deplete hole carriers and reduce the conductance. Hence, NW-FETs can enable real-time label-free direct electrical readout of biological events, including binding/unbinding, enzymatic reactions and electron transfer. These detection capabilities are ideal for developing a platform system for analyzing biological samples.

Semiconductor NWs composed of Si or other materials (e.g., ZnO, SnO_2 and In_2O_3) have been explored extensively as FET sensors [8–10]. Among these NW materials, the potential to achieve molecular-size diameters [11], high electron or hole mobility [12], and versatile surface functionalization of SiNWs [13], as well as the potential of interfacing with existing mature silicon industry processing, have made SiNWs one of the most widely studied for biomolecular sensing [3–5]. SiNW-FETs are transformed into nanosensors by surface functionalization with probe molecules that enable the specific recognition of chemical/biological molecule targets. Covalent binding to the native silicon oxide (SiO_2) layer that naturally grows on SiNWs represents one of the most robust approaches for probe attachment and takes advantage of the wealth of knowledge available from studies focused on functionalization of glass (SiO_2) slides [14]. A detailed surface functionalization process is described elsewhere [13]. The simplest and earliest established example of this approach is hydrogen–ion concentration detection or pH sensing [8]. In this case,
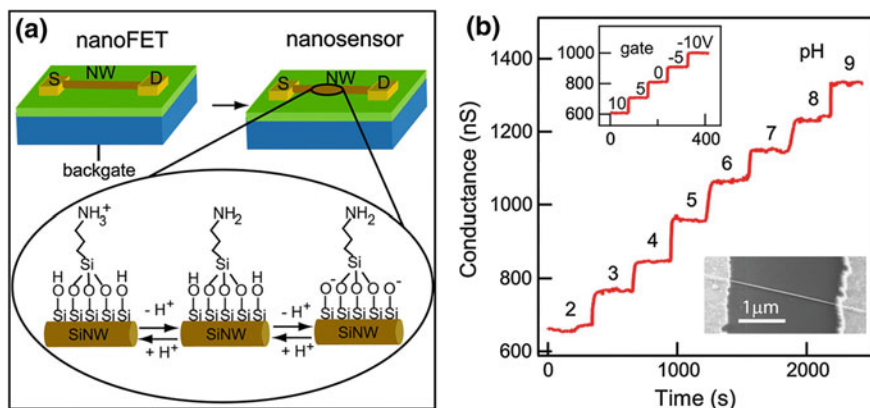
Fig. 10.2 a Schematic of a functionalized NW device and the protonation/deprotonation process that changes the surface charge state. **b** Changes in NW conductance versus pH. Reproduced from [8]. Copyright 2001 the American Association for the Advancement of Science (color figure online)

the SiO_2 layer at a p-SiNW surface is modified with 3–aminopropyltriethoxysilane (APTES), which yields amino group (–NH_2) termination on the NW surface (Fig. 10.2a). The amino groups and silanol groups (Si-OH) on the unreacted regions of the oxide layer undergo protonation and deprotonation as the hydrogen-ion concentration varies, thereby changing the surface charge and the NW conductance. The NW electrical conductance shows a stepwise, discrete and stable increase, in response to increasing pH from 2 to 9 (Fig. 10.2b). More recently, Noy and coworkers demonstrated SiNW-FETs modified with lipid bilayers with and without ligand-gated and voltage-gated ion channels to monitor the solution pH. For lipid bilayer containing ion channels, devices responded to changes in solution pH, and when the channels were blocked the device response was strongly diminished [15]. Sensing studies of several distinct classes of biological targets are discussed below.

10.3 Examples of Nanoelectronic Sensors

10.3.1 Protein Detection

The sensitive detection of proteins, especially those known as disease markers, offers substantial potential to benefit disease diagnosis and treatment. In 2001, pioneering work demonstrated real-time protein sensing with SiNW-FET device [8]. Specifically, SiNWs functionalized with biotin receptors were used to selectively detect streptavidin at concentrations down to 10 pM, substantially lower than other methods at the time. However, the strong binding affinity between biotin and streptavidin leads to effectively irreversible binding and precluded monitoring

unbinding and sequential measurements at different streptavidin concentrations. To overcome this limitation, several reversible surface modifications have been explored, including biotin–monoclonal antibiotin binding and calmodulin (CaM)-Ca^{2+} interaction, to investigate quantitative concentration-dependent analyses [8]. In a more recent study [16], CaM–modified SiNWs are used to detect Ca^{2+} and CaM–binding proteins through the association/dissociation interaction between glutathione and glutathione S–transferase. In addition, this basic approach has been used to demonstrate successful concentration-dependent detection of cardiac troponin T [17] (a biomarker for myocardial infarction), SARS virus nucleocapsid proteins [18], and bovine serum albumin [19] in recent literature and thus further validate the efficacy of NW-FETs as protein sensors.

In genomics and proteomics research, simultaneous detection of multiple proteins is believed to be especially important for diagnosing complex diseases such as cancers [20, 21]. Moreover, the availability of different biomarkers matched with different stages of diseases could allow for early detection and robust diagnosis. Early work on SiNW-FET devices [8], although powerful in detecting binding/unbinding of proteins, lacked the capability of selective multiplexed sensing. To address this issue, Zheng et al. [22] developed integrated NW sensor arrays, in which ~ 100 individually addressable NW-FETs were functionalized with several different receptors (Fig. 10.3a), and demonstrated several new sensing capabilities. Specifically, monoclonal antibodies for the cancer marker proteins prostate specific antigen (PSA) carcinoembryonic antigen (CEA) and mucin-1 were used to functionalize SiNW-FETs in the same device array (Fig. 10.3b). Upon addition of buffer solutions containing different concentrations of these cancer biomarkers,
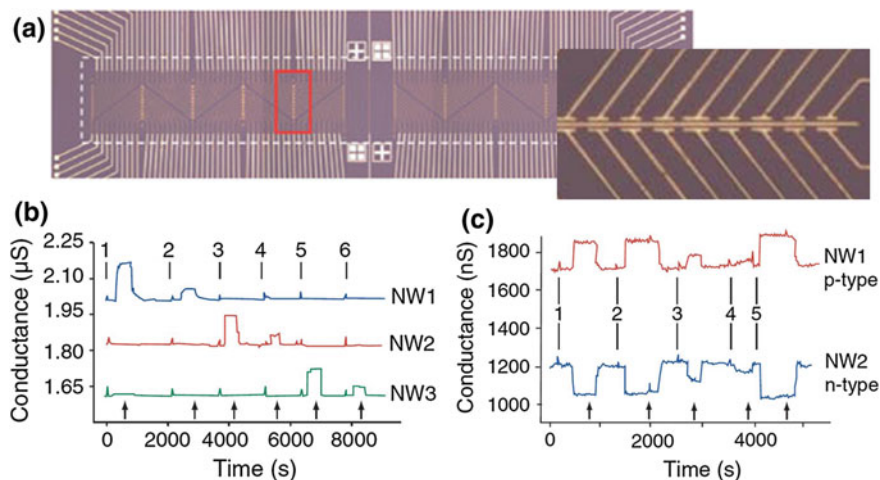

Fig. 10.3 **a** Optical image of a NW array. **b** Sequential detection of PSA, CEA and mucin-1 solutions using three SiNW-FET sensors. **c** Complementary sensing of PSA using a *p*-type (*NW1*) and a *n*-type (*NW2*) SiNW-FET sensors in a same array. Reproduced from [22]. Copyright 2005 Nature Publishing Group

changes in electrical conductance of the corresponding NW-FETs were recorded with femtomolar sensitivity, which is several orders of magnitude better than possible with the standard enzyme-linked immunosorbent assay (ELISA) [22]. This work also introduced the new concept of incorporating both *p*-type and *n*-type NWs into the same device array (Fig. 10.3c). In so doing, the binding of a negatively charged biomarker such as PSA on the NW sensor surfaces led to an increase in conductance for *p*-SiNWs and a decrease for the *n*-SiNWs in the same sensor chip. These complementary, opposite electric signals can be used to distinguish false positive signals and enable real-time, highly sensitive and selective detection of multiplexed biomolecule targets. Similarly, Li et al. [9] reported the complementary sensing of PSA using *n*-type In_2O_3 NWs and *p*-type carbon nanotubes. The enhanced electrical conductance for the NW sensors and the suppressed electrical signal for the carbon nanotube sensors upon the PSA addition are demonstrated with concentrations down to 5 ng/mL sensitivity at physiological buffer concentrations.

Later, an anisotropic wet-etch fabrication method was reported as an alternative 'top-down' NW device fabrication strategy for NW-FET sensors [23]. The sensitivity of these top-down fabricated SiNW devices were shown to have sub–100 fM sensitivity for biotin–streptavidin interaction, mouse immunoglobulin G (IgG), and mouse immunoglobulin A (IgA) detection.

10.3.2   *Nucleic Acid Detection*

In addition to detection of protein binding/unbinding, real-time detection of nucleic acids (e.g., DNAs and RNAs) has been successfully carried out using Si and GaN NW-FET devices [24–27]. The surface functionalization methods and detection schemes used in these studies were similar to those described above for protein sensing, where nucleic acid concentration is transduced following binding to a probe by changes in device conductance. A major difference between nucleic acid and protein detections exists in the fact that the high density of negative charges on the nucleic acid phosphate backbones requires high ionic strength buffers to screen the repulsion and allow for binding when DNA or RNA is used as the probe molecule. However, high ionic strength solutions have short Debye screening lengths (see Sect. 10.4.3), which can make difficult or preclude detection. A solution that overcomes this high ionic strength binding/screening issue involves using neutral charge peptide nucleic acids (PNAs) [28, 29], which exhibit excellent binding affinity with DNA at lower ionic strengths. Indeed, modification of SiNWs with PNA probe molecules was shown to exhibit time-dependent conductance changes associated with selective binding of complimentary target DNA at concentrations as low as 10 fM. Moreover, this work showed that a DNA SiNW-FET biosensor could be used to distinguish fully complementary (wild type) versus single-base mismatched (mutant) DNA targets associated with Cystic fibrosis [25]. Additional studies using SiNWs functionalized with PNA probes in which the DNA target binding domain distance was changed exhibited a reduction in sensitivity

with increasing distance between the hybridization site and the NW surface [30]. This observation is consistent with basic sensing mechanism since the 'field effect' is reduced for fixed charge as the separation from the SiNW surface increases.

An alternative approach for surface functionalization of SiNW surfaces for DNA detection involves electrostatic adsorption of the probes. For example, Bunimovich et al. [31] reported electrostatic adsorption of primary DNA probe strands onto an amine-terminated SiNW surfaces, where the ∼parallel orientation of the DNA probes along the NW surface reduces Debye screening effects and can thereby yield sensitive DNA detection.

More recently, detection of other nucleic acid targets, such as microRNAs (miRNAs) have been carried out using PNA-modified SiNWs. Focus on microRNAs (miRNAs), which are a large class of short, noncoding RNA molecules that regulate animal and plant genomes, is intriguing because they have been proposed as biomarkers for cancer diagnosis [32]. PNA-functionalized SiNW devices have shown the capability to detect miRNAs down to a remarkable sensitivity of 1 fM [33], ca. one order of magnitude better than reported earlier for DNA detection [30]. This phenomenon can be attributed to the higher thermal stability and melting temperature of PNA–RNA complex than that of PNA–DNA complex. The technique enabled identification of fully complementary versus one-base mismatched miRNA sequences, as well as detection of miRNA in total RNA extracted from HeLa cells, and thus offers substantial potential as a new diagnostic tool.

10.3.3 Virus Detection

Viruses are a major cause of infectious diseases and remain the world's leading cause of death [34]. Successful treatment of viral diseases often depends upon rapid and accurate identification of viruses at ultralow concentrations. The first demonstration of nanoFET based virus sensors involved the detection of influenza A virus using SiNW devices. By recording the electrical conductance changes upon binding/unbinding of virus particles to monoclonal antibody-modified SiNWs, the selective detection of influenza A at the single particle level was demonstrated [35]. The binding kinetics between different virus–receptor interactions were also electrically differentiated by SiNW-FETs (Fig. 10.4). In addition, simultaneous detection of influenza A and adenovirus using independent SiNW biosensors functionalized with distinct antibodies for these two types of viruses was demonstrated [35], and more recently, SiNW-FET based selective detection of influenza A viruses down to 29 viral particles per micro-liter was achieved for breath condensate samples [36]. These achievements represent important proof-of-concept steps towards powerful viral diagnostic devices.

Another example of virus detection was the diagnosis of Dengue, a arthropod-borne viral infection [37]. In this latter work, a specific nucleic acid fragment with 69 base pairs derived from Dengus serotype 2 virus genome
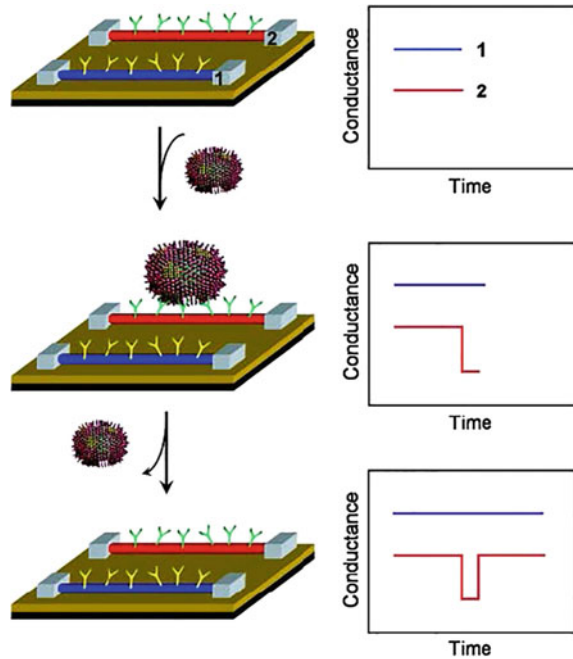
sequence was selected as the target DNA and amplified by the reverse transcription polymerase chain reaction (RT-PCR). The hybridization of the target DNA and PNA-functionalized SiNW-FET sensors increases the device resistance, leading to a sensitivity limit down to 10 fM.

10.3.4   Small Molecule Detection

Detection of small molecules that bind specifically to proteins is of vital importance to drug discovery and screening. One example of small molecule detection involves the identification of adenosine triphosphate (ATP) binding, and the small-molecule inhibition of ATP binding to the tyrosine kinase, Abl, which are proteins that mediate signal transduction in mammalian cells. Gleevec, which competitively inhibits ATP binding to Abl, has been used to monitor binding/unbinding behaviors of ATP. The gleevec concentration at fixed ATP concentration yields conductance decrease, which is consistent with reversible competitive inhibition of an agonist (ATP) with an antagonist (Gleevec) [38]. In a different direction, highly ordered flexible SiNW films, have been applied to detect NO_2 with parts-per-billion (ppb) sensitivity [39]. Other small molecules, such as ammonia (NH_3), acetic acid (AcOH) [40] and 2,4,6-trinitrotoluene (TNT) [41], have also been successfully detected by surface–functionalized SiNW-FET sensors.

Despite numerous approaches developed for achieving highly sensitive detection of polar molecules, the detection of nonpolar volatile organic compounds (VOCs) still remains challenging, due to the weak adsorption of nonpolar VOCs on the surface of NWs and the lack of suitable nonpolar organic functionalities that can be attached to the SiNWs. To address this issue, silane monolayers with a low fraction of Si–O–Si bonds between the adjacent molecules were used to modify SiNW-FETs to enhance their sensitivity towards nonpolar VOCs [42]. In another work [43], it was demonstrated that multiple independent parameters of a specific molecularly modified SiNW-FET can provide high selectivity towards specific VOCs in both single-component and multi-component environments as well as estimating the constituent VOC concentrations.

10.4 Methods for Enhancing the Sensitivity of Nanowire Sensors

10.4.1 3D Branched Nanowires for Enhanced Analyte Capture Efficiency

3D branched NWs [44–49] in which secondary NW branches are grown in a radial direction from a primary NW backbone, provide a number of unique capabilities including a substantially-enhanced surface area compared to the backbone alone. By functionally encoding at well-defined branch junctions during synthesis, rationally designed and synthesized branched NWs can provide well-controlled variations in the composition of the NW backbone and branches, and thus allow for complex electronic and photonic nanodevices. Focusing on sensing, Jiang et al. [47] developed the general synthesis of branched, single-crystalline semiconductor NW heterostructures, including Si backbones with Au branches. The Au-branched NW devices were investigated as nanoelectronic sensors for biomolecular detection (Fig. 10.5). The Au branches, which can be modified in a highly-specific manner using thiol chemistry, can be considered as receptor-functionalized "antennae" for biomolecular analytes. The high surface area of the Au branches provides the potential for enhanced capture efficiency, and thereby can increase the overall device sensitivity. For example, a sensitivity of 80 pg/mL for PSA detection was obtained from mAb-modified p-Si/Au-branch NW-FET sensors, with high selectivity.

10.4.2 Detection in the Subthreshold Regime

The fundamental characteristics of NW-FET devices, such as the transconductance and noise, can have substantial effect on the ultimate detection sensitivity. Conventionally, nanoFET-based sensors are operated in the 'ON' state (above the
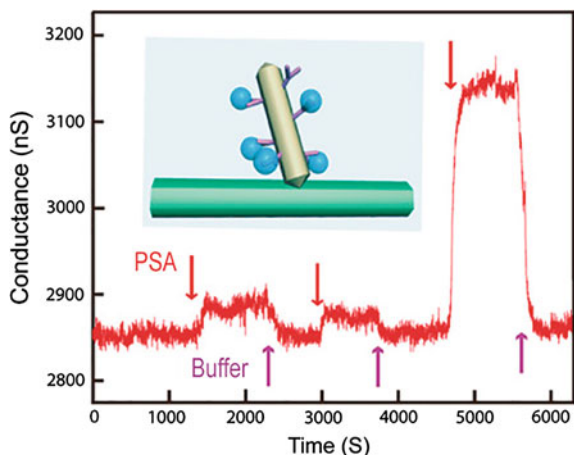
Fig. 10.5 Conductance versus time curve recorded on a *p*–Si/Au branched NW sensor with alternate delivery of PSA (4 ng/mL, 80 pg/mL, 200 ng/mL) and pure buffer solutions. The *top and bottom arrows* mark the delivery of protein and buffer solutions into the sensing channel, respectively. Inset: schematic of Si/Au branched NW sensor. Reproduced from [47]. Copyright 2011 the National Academy of Sciences of the United States of America (color figure online)

threshold voltage), where the transconductance depends linearly on gate-voltage or surface potential. However, in the subthreshold regime it is well-known that the device conductance depends exponentially on gate-voltage [50], which could in principle lead to much higher analyte binding sensitivity. Indeed, Gao et al. [51] studied and compared the detection sensitivity of SiNW-FET sensors in the linear and subthreshold regimes (Fig. 10.6). In previous literature using SiNW-FET sensors [8], the conductance change (ΔG) or the resistance change (ΔR) of the sensor devices was used to quantify the concentration of the target molecules. However, an
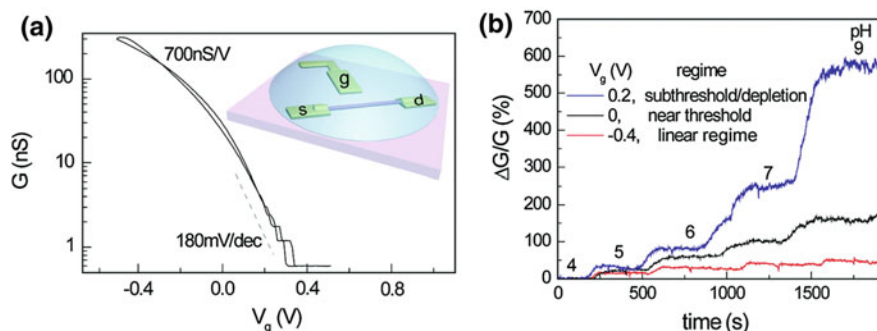

Fig. 10.6 a Conductance, G, versus V_g for a *p*-type SiNW-FET. Inset: scheme for electrolyte gating. **b** Real time pH sensing. The device in the subthreshold regime shows much larger $\Delta G/G$ change versus pH. Reproduced from [51]. Copyright 2010 American Chemical Society

absolute signal change, such as ΔG, does not reflect the intrinsic device sensitivity, especially when working in the subthreshold regime where device conductance is very small. To better compare sensing in different device regimes Gao et al. used a dimensionless parameter, $\Delta G/G$, to characterize and compare device sensitivities. This principle is exemplified in both pH and protein sensing experiments, where the electrolyte gating is used to tune the operational mode of NW-FETs (Fig. 10.6b). These results showed that significant sensitivity enhancement could be achieved by optimization of the FET operating conditions and understanding the fundamental electrical gating property of NW-FETs. One caveat to the success of this work is that the device noise should be dominated by carrier-carrier scattering, such that the noise is also exponentially reduced in the subthreshold regime. If the noise is dominated by other scattering mechanisms, such as contact current injection and/or interface trapping/detrapping, then it may not be possible to exploit the exponential dependence of conductance on gate-voltage/surface potential in the subthreshold regime.

10.4.3 Reducing the Debye Screening Effect

Conventional FET sensors detect the concentration of the target species by their intrinsic charge. The charges of solution-based molecules, however, can be screened by dissolved counter ions in the solution. The Debye length, which is inversely proportional to the square root of the ionic strength of an electrolyte, represents the net or screened electrostatic effect of a charged species in ionic solution. A high ionic strength electrolyte solution leads to a short Debye length, and charges outside of the Debye length are electrically screened. For instance, the Debye length of $1 \times$ PBS, ~ 0.7 nm, can screen most protein antigen charges when they bind to an antibody modified FET surface. In order to reduce the charge screening effect of electrolyte solutions, the Debye length is typically increased by using dilute buffer solutions with low ion concentrations [18, 52].

Recently, several groups have reported approaches based on smaller receptors, such as aptamers [53] or antibody fragments [54] to reduce the distance between the FET surface and the receptor-bound biomolecule analyte. In one example [54], the sizes of antibody probes were reduced through common biochemical methods (Fig. 10.7), thereby improving the analyte detection capability. These studies are promising, although further studies are needed to determine how general detection is under the limit of physiological conditions (Debye length <1 nm) as the sizes of the aptamer and antibody fragment receptors are similar to or greater than this critical length scale. Zhong and co-workers [55] also reported a direct high-frequency measurement strategy for standard biological receptors, although those measurement requires significantly more complex device geometry, making difficult or precluding application to cellular and in vivo sensing.

Recently, Lieber and coworkers [56] developed a new and general strategy to overcome this challenge for NW-FET sensors that involves incorporating a biomolecule permeable polymer layer, such as polyethylene glycol (PEG), linked to
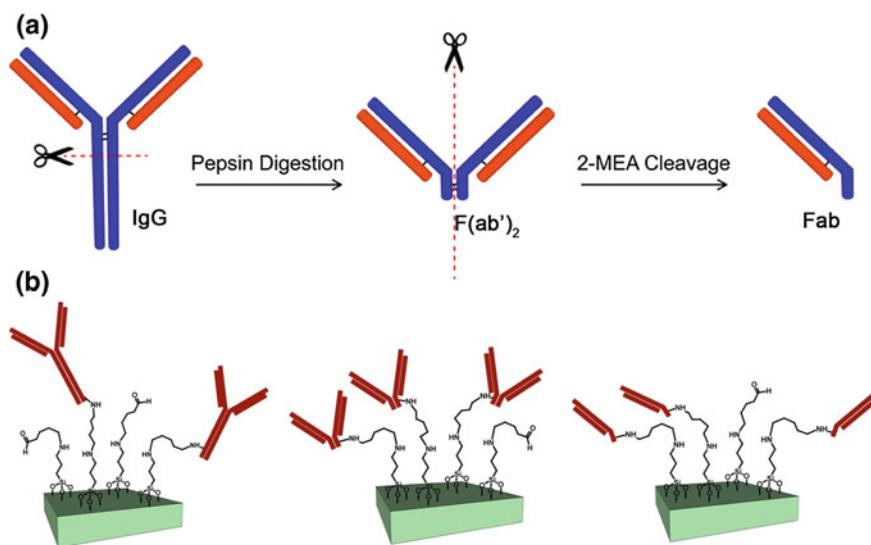
Fig. 10.7   a Schematic for the generation of F(ab')$_2$/Fab fragments from a whole IgG molecule. **b** Schematic for the immobilization of a full IgG, F(ab')$_2$ and Fab antibody-fragments which contain free amine groups onto the SiO$_2$ surface as receptor layers. Reproduced from [54]. Copyright 2012 American Chemical Society

the FET sensor, where the polymer increases the effective screening length near the NW-FET surface to allow for detection in high ionic strength solutions (Fig. 10.8a). Using PSA as a model system, they showed that PEG-coated SiNW-FETs can detect PSA in phosphate buffer concentrations up to 150 mM, with a detection
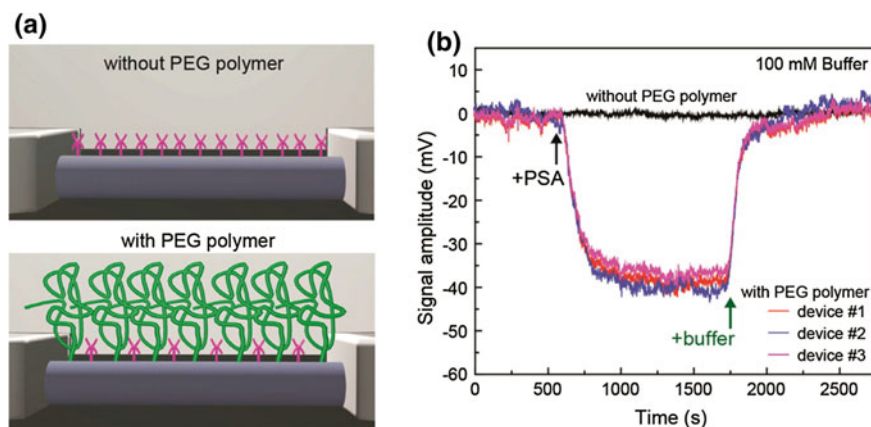

Fig. 10.8   a Schematic illustration of a NW-FET device (*top*) without and (*bottom*) with a porous and biomolecule permeable PEG surface modification. **b** Comparison of signal response traces recorded from three SiNW-FET devices with and one device without PEG modification. Reproduced from [56]. Copyright 2015 American Chemical Society

sensitivity of ~ 10 nM and linear response range up to 1000 nM. In contrast, similar FETs without PEG functionalization can only detect PSA in buffer salt concentrations lower than 10 mM (Fig. 10.8b). This work suggests a new and general device design strategy for the FET sensor applications in physiological environments, important for in vitro and in vivo biological sensing.

10.4.4   Electrokinetic Enhancement

Concentration of analyte near a device surface by electrokinetic effects offers another approach for high-sensitivity protein detection [57]. In a nonuniform alternating current (AC) electric field, the dielectrophoresis (DEP) force can induce polarized particles to move in a directed manner leading to the formation of concentration enhancement and depletion regions in a microfluidic flow channel. Compared to the detection limit without AC excitation, NW sensors modified with monoclonal antibodies for PSA in an appropriate AC field exhibit close to a $\sim 10^4$ fold increase in sensitivity; that is, the protein concentration at the sensor surface is increased by DEP. In addition, NW devices functionalized with other receptors for capturing cholera toxin subunit B were also demonstrated, suggesting the general applicability of this method for enhanced sensitivity detection [22, 57, 58]. It is important to recognize, however, the DEP enhancement, including frequency response, depends sensitively on solution ionic strength [58, 59].

10.4.5   Frequency Domain Measurement

In addition to the conventional real time measurement device conductance to monitor sensing, frequency-dependent fluctuations in the NW-FET electric signal at equilibrium can convey additional information about the dynamics of the biomolecule-NW hybrid system through a coupling to carrier transport in the device to binding events. For example, binding and unbinding can affect the intrinsic device noise, and thus can be characterized through measurements of the frequency-dependent noise spectra (Fig. 10.9a) [60]. In a recent study, the noise spectra was used to analyze contributions from different noise sources [60]. The frequency domain spectrum of a fluctuating two-level system has the form of a Lorentzian function similar to that of a *RC* circuit (Fig. 10.9b and c). The $1/f$ noise is well-known in conventional metal–oxide semiconductor FETs (MOSFETs), and arises from electron capture/emission from trap states [61, 62]. If biomolecule binding/unbinding contributes substantially to the noise, it can leads to a Lorentzian peak in addition to the $1/f$ background. Specifically, a *p*-type SiNW-FET was first modified with PSA monoclonal antibodies, then solutions with different PSA concentrations and pure buffer were sequentially delivered to the NW sensor via a microfluidic channel. In conventional time-domain measurements (Fig. 10.9d), a
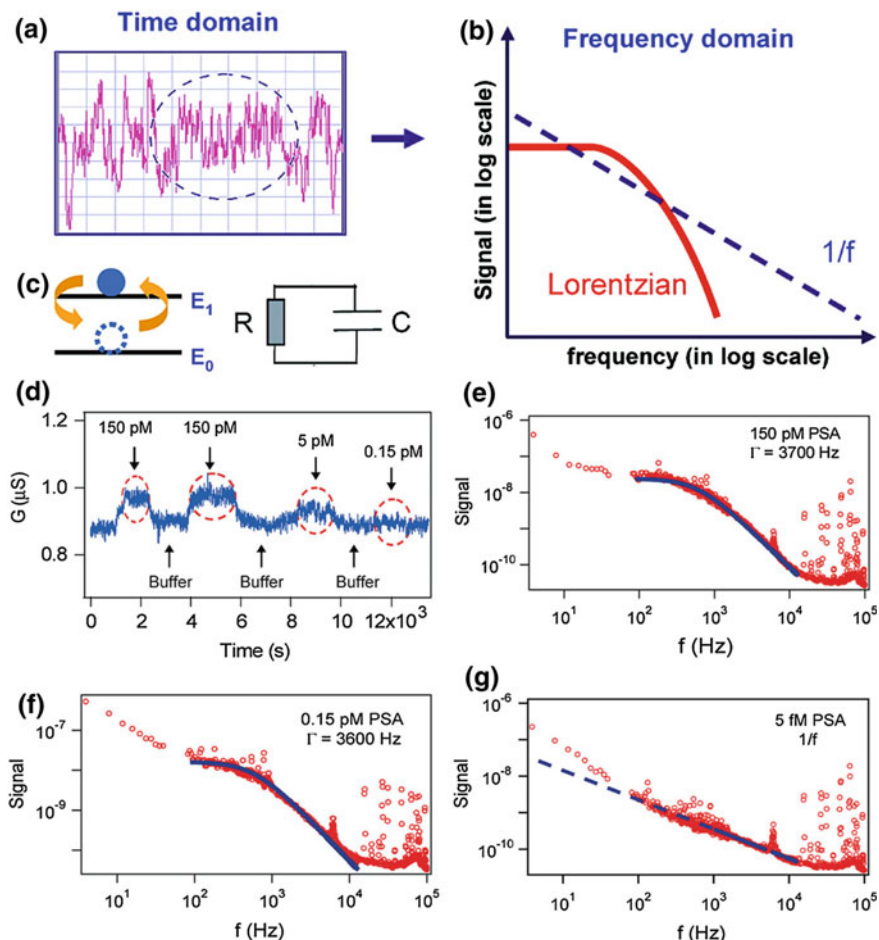
Fig. 10.9 a Electrical noise in a time-domain measurement. **b** Lorentzian and 1/f functions in the frequency domain. **c** Models of a two-level system (*left*) and a *RC* circuit (*right*). **d** Time domain conductance measurement of a *p*-type SiNW-FET sensor modified with PSA monoclonal antibodies, when different concentrations of PSA solutions were delivered to the sensor. **e–g** Power spectra recorded in solutions with different PSA concentrations, 150 (**e**) and 0.15 pM (**f**), show Lorentzian shape curves, while power spectrum recorded in 5 fM PSA solution shows a 1/f frequency dependence (**g**). Reproduced from [60]. Copyright 2010 American Chemical Society

reliable PSA detection limit for this device was ca. 5 pM. However, the frequency domain noise spectra (Fig. 10.9e–g) from the same NW-FET device showed that the Lorentzian curve shape was still clearly observed at a PSA concentration as low as 0.15 pM, ca. 30 times better than that the same device measured in the time domain. The improved detection sensitivity was attributed to the separation of the Lorentzian characteristic frequency from the most dominant background of 1/f noise, which becomes less important at high frequencies.

10.4.6   Nanowire–Nanopore Sensors

The integrated NW–nanopore FET sensor has the potential for single-molecule DNA sequencing at low cost and with high throughput [63]. The conventional nanopore DNA sequencing technique records ionic current from nanopores [64], while NW–nanopore sensors allow for direct sequencing of DNA molecules with fast translocation rates given the much higher bandwidth of NW-FETs.

Studies have shown that nanopores can be introduced adjacent to SiNW-FETs using the focused electron beam in a transmission electron microscopy (TEM) [63] (Fig. 10.10a). A sensor device can then be configured by attaching PDMS solution reservoir chambers above and below the silicon nitride membrane on which the SiNW-FET nanopore devices are fabricated. When the two chambers are filled with solutions of different ionic strength, FET signals corresponding to DNA transloca-tion events can be reproducibly recorded (Fig. 10.10b and c). Notably, a 10–60 times higher signal was observed from the SiNW-FET than that of the corresponding ionic current change in these studies. This work demonstrates a new nanopore sequencing device concept with fast sequencing and large-scale integration properties.
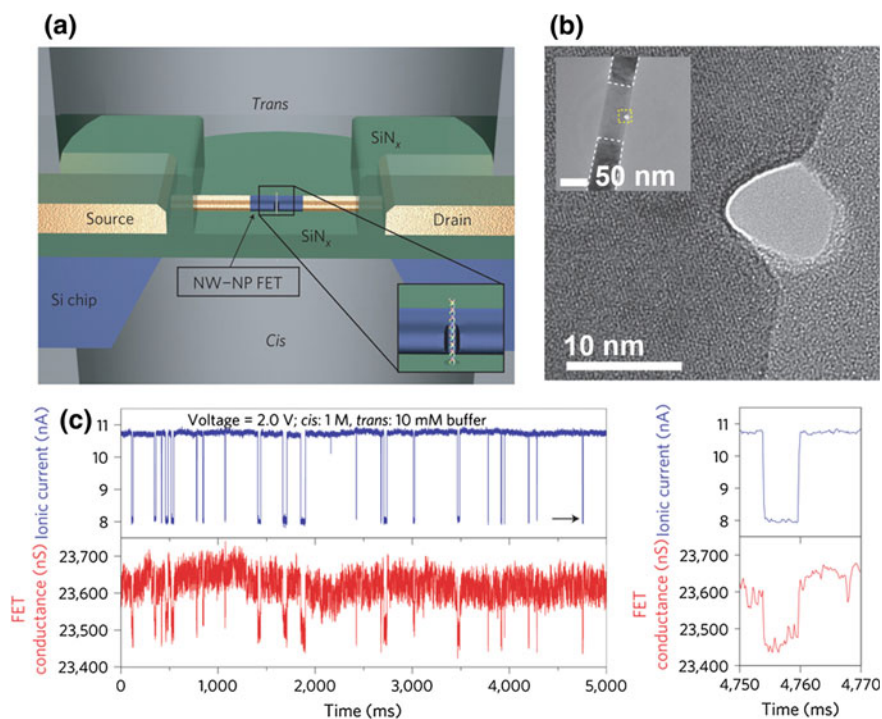

Fig. 10.10   a, b Schematic and TEM image of a SiNW–nanopore sensor. **c** Recording of SiNW–nanopore FET conductance and ionic current during DNA translocation. Reproduced from [63]. Copyright 2012 Nature Publishing Group

10.4.7   Double-Gate Nanowire Sensors

In order to achieve higher sensitivity NW-FET sensors, extensive effort has been focused on advanced device designs prepared by top-down lithography [65, 66]. For example, several groups have fabricated and explored double-gate NW-FET biosensor, with two separated gates, G1 (primary) and G2 (secondary), straddling both sidewalls of the SiNW, to enhance device sensitivity [65, 66]. This work has shown that by applying the same voltage to G1 and G2, the threshold voltage (V_T) in the double gate mode is very sensitive to a small change of V_{G2} (the G2 voltage). Therefore, compared to a single-gate FET sensor, the sensing window of the double-gated FET is significantly broadened, especially in the subthreshold regime described earlier.

10.4.8   Detection of Biomolecules in Physiological Fluids

Rapid and accurate molecular analysis in physiological fluids (i.e., blood or serum) is essential for disease diagnosis and management. NW-FET sensors have routinely demonstrated ultrasensitive, real-time, multiplexed detection biomolecular species, but also have limitations with respect to sensing in complex, physiological solutions as describe in Sect. 10.4.3. To reiterate, the primary limitation for FETs is related to Debye screening effect [67] in high ionic strength blood/serum samples.

   To overcome the limitation of Debye length, researchers have developed several methods to detect analytes in blood/serum samples, including simply reducing the solution ionic strength. For example, the ion concentration can be reduced by diluting a blood sample with buffer solution [68]. Dilution will reduce analyte concentration and can affect ligand- and protein-protein interactions, and thereby reduce device sensitivity. A second approach involves desalting the serum samples before detection of biomarkers [22], which can maintain or even be used to increase analyte concentrations (after dissolution in buffer). Similar to off-chip desalting using rapid size-exclusion chromatography [22], a microfluidic purification chip (MPC) can be used to pre-isolate the target molecules and then release them into a pure buffer suitable for analysis using SiNW-FET arrays [69]. A fourth method adopts a steady-state measurement instead of a real-time recording [70]. Specifically, the resistance of the SiNW is measured in a low ionic strength buffer solution after antibody functionalization. Then, the SiNW sensor is incubated with undiluted serum and subsequently washed to remove unbound proteins, followed by the measurement of the second resistance value in the buffer solution. The concentration of the target molecules can be calculated according to the resistance change before and after antibody–antigen interaction. This method is independent of the ionic strength of the sample solution, thus circumventing the Debye screening in physiological fluids; however, it is subject to variations in device properties between steps since slow changes in background conductance are not

followed. Other reported methods include using smaller receptors, such as aptamers [53] or antibody fragments [54], and adding biomolecule permeable polymer layers to the FET sensor [56], as discussed in Sect. 10.4.3.

The long-term stability of the NW nanoelectronic devices in physiological studies has also been investigated [71]. Coated with a thin layer of Al_2O_3, SiNW-FETs yield long-term stability (>4 months) in physiological model solutions at 37 °C. Notably, coating with Al_2O_3/HfO_2 layers has suggested that an even longer of stability of >1 year is possible for SiNW-FETs in physiological model solutions. These latter results suggest the potential of the SiNW-FETs for long-term chronic in vivo studies in animals and biomedical implants.

10.5   Future Directions and Challenges

Over the last decade, remarkable research progresses have been achieved on the design and implementation of semiconductor NW sensors. In this chapter, we have illustrated how the NW-based FET sensors modified with specific surface receptors represent a powerful chemical/biomolecule detection platform. The examples described here summarize several unique capabilities for direct, label-free, real-time, ultrasensitive and highly selective multiplexed detection of proteins, nucleic acids, viruses, and small molecules, and show clearly the potential of these materials and devices to significantly impact disease diagnosis, genetic screening, and drug discovery, as well as offering powerful new tools for research in many areas of disease diagnosis and life sciences.

Nonetheless, there are several areas of scientific study, which if addressed, could further push the limits of this technology for applications. First, one fundamental challenge to the ultrasensitive detection is to obtain well-defined receptor structures on nanodevice surfaces. In part, this reflects difficulties in characterizing receptor–device structure at the single nanodevice level and correlating such results with sensing results. One approach that could address this structural issue at the single device level would be by exploiting the substantial advances in cyro-EM [72, 73], which could yield high-resolution structural information of the organic/biologic/nanodevice interface. A second direction that could improve this critical device-receptor interface would be through exploration of highly-selective, self-limiting covalent chemistry that precisely defines distance and orientation of the receptors. Second, the real-time and multiplexed detection capabilities of nanoelectronic FET sensors for direct analyses of whole blood/serum detection could yield important advances in clinical monitoring and diagnostics. As discussed in Sects. 10.4.3 and 10.4.8, the most critical issue has been overcoming Debye screening in physiological solutions. The new strategy of modifying FET nanodevices with a permeable polymer layer to increase the effective screening length [56] is one promising strategy for achieving real-time detection, although further fundamental studies will be necessary to develop this and/or other approaches to the level of a technology. Third, almost all the nanoFET-based sensors are exclusively

surface-bound devices. For many applications, one of the most impactful directions could be the transformation from on-chip signaling to the in vivo monitoring as an implant. Recent advances in the development of NW-FET arrays embedded in engineered tissue patches [74], which could be implanted, and incorporation of sensors in injectable electronics [75], which is directly implanted in specific tissue, could enable the goal of direct in vivo monitoring.

In the next decade, continued efforts to achieve the capability in controlling the mechanisms of the NW sensor arrays will move beyond current technologies and take advantage of information emerging from genomics and proteomics to improve the diagnosis and treatment of cancer and other complex diseases. We believe that these advances can be developed in simple NW sensor devices that would represent a clear application of nanotechnology and, more importantly, a substantial benefit to the society.

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