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Synergy between biochemistry, medicine, and material science during last decade has led to a tremendous scientific progress in the fields of biodetection and nanomedicine. This tight interaction led to the emergence of a new class of bioinspired systems. These systems are based upon utilizing nanomaterials such as nanoparticles, carbon nanotubes, or nanowires as transducers for producing novel sensor devices, or sophisticated drug delivery agents. This chapter focuses on the developments made in the area of silicon nanowire-based devices and their applications in the diverse areas of nano- and biotechnologies. Firstly, the incorporation of silicon nanowires into the electrical circuits is discussed, together with the sensing mechanism of the devices. In particular, the discussion is directed toward the most important aspects of the fabrication and functioning of the sensors, as well as the issues regarding the organic molecules interfacing with the silicon surface. Moreover, the complex interactions of organic species with nanoscale matter are addressed to as well as the need for sophisticated integration and packaging of the subsystems on a single chip. Finally, the perspectives of the potential applications of the silicon nanowires for biodetection and drug delivery are presented. Thus, the concept of "lab on a wire" is introduced as a set of approaches to engineer the nanowires and to enrich their functionality and potential applications in nanoscience and biotechnology.
Chapter 10
Lab on a Wire: Application of Silicon Nanowires for Nanoscience and Biotechnology

Larysa Baraban, Felix Zoergiebel, Claudia Pahlke, Eunhye Baek, Lotta Roemhildt and Gianaurelio Cuniberti

Abstract Synergy between biochemistry, medicine, and material science during last decade has led to a tremendous scientific progress in the fields of biodetection and nanomedicine. This tight interaction led to the emergence of a new class of bioinspired systems. These systems are based upon utilizing nanomaterials such as nanoparticles, carbon nanotubes, or nanowires as transducers for producing novel sensor devices, or sophisticated drug delivery agents. This chapter focuses on the developments made in the area of silicon nanowire-based devices and their applications in the diverse areas of nano- and biotechnologies. Firstly, the incorporation of silicon nanowires into the electrical circuits is discussed, together with the sensing mechanism of the devices. In particular, the discussion is directed toward the most important aspects of the fabrication and functioning of the sensors, as well as the issues regarding the organic molecules interfacing with the silicon surface. Moreover, the complex interactions of organic species with nanoscale matter are addressed to as well as the need for sophisticated integration and packaging of the subsystems on a single chip. Finally, the perspectives of the potential applications of the silicon nanowires for biodetection and drug delivery are presented. Thus, the concept of “lab on a wire” is introduced as a set of approaches to engineer the nanowires and to enrich their functionality and potential applications in nanoscience and biotechnology.

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10.1 Nanowire-Based Sensor Devices

After the decades of intense investigations in the 1980s and 1990s of the last century, nanoscale devices have finally entered the phase of diverse commercial applications, fulfilling needs of the society in even more multifunctional, faster, and smaller electronics. In recent years, the one-dimensional nanostructures, in particular semiconductor nanowires have attracted attention as highly efficient sensor elements due to their high surface-to-volume ratio and one-dimensional structure [1–3] which enables the detection of biochemical species down to single molecules [4–6]. The physical reason for the high sensitivity is to be found in the small diameter of the nanowire, allowing even single molecules to effect the conductivity in the channel by penetrating it with an electric field. This novel nanowire-based technique is capable of not only a real-time and label-free sensing of the very small quantities of the biomolecules, but also provides information on the conformation of the molecules and the strength of the biomolecular interactions. In particular, the binding efficiency of the receptor and analytes, as well as hybridization in the solution, can be tested [7]. These developments in the area of bionanosensorics can potentially become a powerful competitor to the conventional biochemical or optical detection techniques, which currently dominate the market.

Although a single nanowire can detect a single molecule, a binding event is not likely to happen on the tiny wire surface. Furthermore, integration of the nanowire
elements into conventional electronic circuits, expected on the longtime perspective, requires the substantially increased current output of the sensor device. These shortcomings can be overcome with the use of parallel arrays of nanowire sensors. In so doing, the large surface areas can be covered without sacrificing efficiency of the switching behavior. Additionally, by incorporating several hundred nanowires into the parallel array, the yield of functioning transistors can be dramatically increased and device-to-device variability can be reduced compared to that of individual devices.

10.1.1 Design of Sensor Devices: Top-Down Versus Bottom-Up

The essential element of the sensor system is the silicon nanowires (SiNW) assembled as field-effect transistors (FET) and a multitude of techniques has been developed for manufacturing SiNW-based FETs (see Chap. 5). The methods of fabricating field-effect transistors are generally divided into the top-down and bottom-up processes. Figure 10.1 demonstrates the examples of the silicon nanowire devices, processed by both top-down and bottom-up techniques for sensing applications. The top-down manufacturing techniques have already been developed extensively for industrial FET production of microelectronic devices. In this approach, devices are fabricated in a lithographically assisted manner by several consecutive etching and material deposition steps. The approach enables the high-density integration of functional elements on a very small scale, a key point in the development of modern computer technology. As an example, Fig. 10.1a shows an array of ten perfectly aligned nanowires with diameters of about 50 nm, fabricated by means of the top-down nanofabrication processes and integrated with interconnects via monolithic patterning [8].

Fig. 10.1 a Top-down manufacturing: Electron-beam lithography and reactive ion etching produced silicon nanowire FETs with 50 nm diameter [8]; b Bottom-up manufacturing: Parallel array of Schottky barrier silicon nanowire FETs. Inset: Schottky barrier junction, created by thermal diffusion of the metal into semiconductor nanowire [9]
Bottom-up processes, on the other hand, rely mainly on the self-assembly and self-organization of functional elements, such as atoms, molecules, and clusters. A prominent example is the growth of carbon nanotubes from fullerenes or chemical vapor deposition assisted growth of silicon nanowires starting with gold catalyst. The nanowires thus grown can be efficiently integrated into sensor devices by means of much simpler and cost-effective processes. For instance, a contact printing approach for vapor-liquid-solid (VLS)-synthesized SiNWs can be used for transferring etched nanowires to chip substrates [9]. As shown in Fig. 10.1b, the large and high-density arrays of the silicon nanowires can be brought to the substrate and contacted by using ultraviolet lithography to form FET devices. Note that the combination of the bottom-up growth technique of nanowires and the ability to print nanowires at virtually any surface opens a great possibility for bottom-up FETs to be incorporated into a cost-efficient printable and flexible electronics.

10.1.2 Design of Sensor Devices: Single Wire Versus Parallel Array

High current densities and high transconductance, obtained with the silicon nanowire-based FETs, are the crucial parameters, which have yet to be attained to compete with state-of-the-art CMOS technology. For instance, raising the transconductance in nanowires FET to 1 mA/μm would be sufficient to apply the device as a driver for organic light emitting diodes or as transducer with stable outputs for sensors. Thus, the application of the parallel array of nanowire FETs for sensing has a great advantage, since it enables substantial increase in the drain current $I_{ds}$, while preserving the high subthreshold slope in the transfer characteristics.

In order to demonstrate this tremendous tendency, Fig. 10.2 reflects a comparison of transfer characteristics of a single-wire device (top-down fabricated) and a parallel array of Schottky barrier silicon nanowires (bottom-up). The top-down manufactured device shown is a $p$-doped silicon-on-insulator single nanowire device with 20 nm channel height, 400 nm channel width, and 5 $\mu$m channel length. In contrast, the bottom-up manufactured device is a parallel array of 100–1,000 Schottky barrier silicon nanowire FETs with single wire diameter of 20 nm and silicon channel length of approximately 6 $\mu$m. The inverse subthreshold slope of both devices is approximately $-120$ mV per decade of current change for both devices, corresponding to twice of the physically achievable minimum of $-59.9$ mV per decade for hole-conducting FETs.

Moreover, nanowire-based FET devices exhibit excellent switching behavior that is critical for sensing applications (see Chap. 9) at relatively high current even for parallel arrays of hundreds of nanowires.

1 Chips are fabricated and provided by IM Health, South Korea.
10.1.3 Sensing Principle

The basic parameter in FET-based sensors is the gate voltage-induced surface potential, which modulates the channel conduction. The field-effect devices are very efficient transducers of the changes in the surface potential, making it superior to direct potentiometric measurements. The maximum threshold shift is determined by the Nernst equation. Ideally, an FET operating at room temperature should generate the current change of one decade with the gate voltage change of 59.5 mV. However, the imperfect interface at the metal contacts and roughness of the nanowire surface leads to an increase in this number [10, 11]. Any binding event that changes the surface charge or the surface potential due to a chemical reaction or electrostatic interaction will, therefore, be detectable with an FET-based sensor device.

In contrast to the electronic applications, where the gate electrode consists of a metal or semiconductor and is separated from the channel by an insulating dielectric layer, sensing in liquid (as described previously in Chap. 9). In this case, the gate voltage is applied to the measurement solution and dielectric layer can be made of the native oxide of the silicon nanowire or an additional dielectric layer, e.g., hafnium oxide, aluminum oxide, or silicon nitride. In such measurement configuration, an additional back gate can be used to enhance the nominal sensitivity of the devices, [11, 12] without increasing the signal-to-noise ratio.

10.1.4 Example: Schottky-Barrier-Based Bottom-Up Device

Let us consider the operation of Schottky-barrier (SB)-based sensor device, produced by the bottom-up nanofabrication process. The current modulation in Schottky barrier SiNW field-effect transistors arises via the tunneling of the...
voltage-controlled charge through the metal–semiconductor junction. Figure 10.3 shows the corresponding band diagrams, displaying the charge transfer through Schottky contacts. This behavior was first used by Weber et al. in 2008 [13] to control the polarity of the switching behavior of these FETs and further extended by Heinzig et al. in 2012 to build a converter circuit with a single silicon nanowire [14].

It has been recently shown that Schottky junctions play crucial role in the sensitivity of the silicon nanowire field-effect transistors. An evidence that the maximum field sensitivity is localized at the Schottky barriers is demonstrated by Martin et al. in [15] using scanning gate microscopy. An electrical scanning probe technique is applied to examine the charge transport effects of a nanometer-scale local top gate during operation. The results prove experimentally that Schottky barriers control the charge carrier transport in these devices.

Schottky-barrier-based FETs are fabricated using CVD-grown intrinsic silicon nanowires, which are contact printed on a receiver substrate and contacted by interdigitated Ni electrodes in the photolithography step. Schottky barriers are then formed in a bottom-up process by diffusing nickel into the SiNWs at 500 °C in forming gas. The lattice constant of the resulting NiSi2 phase deviates from the lattice constant by only 0.4 % [16, 17], leading to atomically sharp Schottky barriers between the silicon channel and NiSi2 leads. An electron micrograph of silicon nanowires contacted by nickel electrodes with intruded NiSi2 phases is

![Fig. 10.3](image-url) a Schematics of the band diagram of Schottky junction. From top to down: Electron-tunneling modulation in hole conduction state, OFF state, and electron conduction state, respectively. b Scanning gate measurements at a single Schottky barrier silicon nanowire FET, using atomic force microscopy (AFM). Current map of the nanowire region, containing Schottky junction, with voltage applied to the AFM tip. Effects are seen at the Schottky barrier. Images are scanned from Top left to bottom right [15].
shown in Fig. 10.1b. The semiconductor–metal interface is also shown in the inset above.

In order to use such devices for liquid-sensing applications, a layer of isolating layer, e.g., Al₂O₃, was deposited on the entire chip using atomic layer deposition technique. Microfluidic channels should be further placed on the chip and a Ag/AgCl electrode should be attached to the channel in order to apply a gating voltage to the liquid.

The quality of the metal-semiconductor interface is therefore crucial for the function and satisfactory performance of the FET devices. A sharp interface with very low mixing of metal and semiconductor phases must be realized to attain the well-defined interface barrier for tunneling and to obtain the field enhancement effect.

10.1.5 Example: pH Sensor

Sensing of the pH value is a benchmark for the quality of surface potential sensors processed in silicon nanowires. During the device operation, the surface potential is controlled according to the Nernst equation (see Chap. 9). The change in the surface potential adds to the gating potential of the liquid electrode modulating the drain current logarithmically in the subthreshold regime of the FET. The maximum possible change of the drain current per gate voltage was discussed in the preceding chapters. The sensitivity for measurements of the pH value is given by

\[ S = \partial \log_{10} I_{ds} / \partial pH \]

and is limited to |S| ≤ 1. The sensing of the pH values by an FET is generally based on a linear dependence of current and surface charge. However, the sensitivity under discussion depends exponentially on the gate voltage because of the steep current change from OFF to ON states in the subthreshold regime. The low values of the numerator in Eq. (10.1) are due to low subthreshold current level, which in turn leads to higher noise level in electronic measurements. Accordingly, the sensitivity is not only dependent on device quality, but also on the measurement scheme. This point was first investigated by Gao et al. in 2010 [10].

The authors showed that the pH sensing can be optimally done by operating the sensing FET in the subthreshold regime. Because of the efficient sensing capability, a multitude of silicon nanowire-based biological sensors has been reported in recent years, which suggests viable commercial applications in the near future [5, 6, 18, 19] (Fig. 10.4).

Quantitative pH sensing requires more than the measurement of the changes in drain current. Rather the surface potential, which is linearly dependent on the pH value for ideal surfaces, should also be monitored. This is done by monitoring continuously the changes in gate voltage to keep the drain current pinned at a given fixed level. For an ideal liquid electrode, the measured change in gate
voltage reflects the negative change of surface potential. This is because any change in the surface potential must be compensated by the potential in the liquid-gate electrode in order to keep the gating potential in the wire constant.

10.2 Nanowires as Element of Hybrid Circuits

The development and commercialization of novel hybrid intelligent systems with rich functionalities, providing strong benefit in the area of health care, environmental monitoring, and electronic applications are among the most crucial topics of the scientific community and industrial players. Recent developments in synthetic chemistry, physics, bioengineering, and nanosciences allow us to envision the appearance of novel hybrid nanoelectronic devices on a market already in the near future. Nanowires can provide excellent building blocks for hybrid nanoelectronics, due to their efficient charge transport characteristics and good compatibility with molecules. Hybrid nanowire-based devices rely on inorganic circuitry, combined with organic molecules. The molecular conjugation with nanowires has been demonstrated and recent studies focus on employing

**Fig. 10.4** pH sensor based on silicon nanowire FET. a Electric switching characteristics of a doped silicon nanowire sensor device. b pH sensitivity for different gate voltages. c Normalized data from (b) for comparison. d Relative signal change versus pH value for all gate voltages [10]
outstanding features of molecules onto the nanoelectronic devices. These hybrid devices are applied for memory or logic circuits driven by light. Light-induced switching of molecules acts as electrical gating of nanowire transistors to drive conductance changes in nanowires to induce conductance changes from OFF to ON states or vice versa.

10.2.1 Organic Molecules in Conjunction with Silicon Nanowires

Recently, there have been huge interests in studies of electrical conjunction between organic molecules and metal or semiconductor surface. For the case of silicon-based devices, a variety of well-established fabrication processes are available for use and the energy-band structures are also well known. Therefore, investigations of molecular functionalization of silicon and, in particular, SiNW surface have been extensively carried out for practical optoelectronic applications. Thus, understanding of interfacial interactions between molecular layer and silicon surface is rather important for analyzing and fabricating molecular hybrid devices.

Photochromic molecules are transformed by light between two or more stable isomers possessing different absorption spectra and geometry. The isomers are converted from one form to another under light irradiation with proper wavelength and revert to original state thermally or by light with different wavelength [20–22]. There is wide variety of the photochromic dyes, i.e., azobenzenes, diarylethenes, spiropyranes, fulgides, which are actively investigated during last decades. Chemical structures of these molecules are presented in Fig. 10.5. Chemical conformations of these molecules are changed by absorption of UV light and are converted back to original states by absorption of visible light or by thermally activated process.

In addition to the above-mentioned photochromic molecules, natural organic complex porphyrin has emerged as the most popular molecule for hybrid application due to its well-known and interesting characteristics. Porphyrin is easily found from living organism such as chlorophylls and Hemes. Single- and double-bond array forming porphyrin ring absorbs broad wavelength range of visible light (Fig. 10.6). Once irradiated by light of specific wavelengths in optical range, \( \pi \)-electrons participating in the bond array are released and move easily through molecular bonding [23].
To understand electronic structure between molecules and solid surface, consider the molecular energy-band diagram [24]. Figure 10.7a shows electronic structure of hydrogen atom and naturally the electron occupies the lowest 1s orbital. The electron can escape from the atom to the vacuum level (VL). In a molecule, deep atomic orbitals are localized in atomic potential well, but higher lying orbitals interact with each other to form molecular orbitals, that is, the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (Fig. 10.7b). When molecules are located in close vicinity to each other, they interact via the weak van der Waals interactions, so that LUMO and HOMO are localized in each molecule (Fig. 10.7c). Therefore, the application of typical band theory is limited to molecular solid that has existing single-molecular electronic structure. Figure 10.7c can be simplified to Fig. 10.7d and e.
The band diagram of an interface between silicon and organic molecules is shown in Fig. 10.8a. The work function of silicon ranges from 4.6 to 4.8 eV and the energy gap $E_g$ is about 11 eV [24]. The HOMO–LUMO gap of organic molecules that absorb visible and ultraviolet light is around 1.5–3 eV. The ionization energy of photochromic molecules from HOMO to the vacuum level is in the range of 4–7 eV. Silicon surface states are important for charge distribution, because they act as acceptor or donor states and surface states are coupled to the molecular layer via the charge exchange to align the Fermi level at equilibrium (Fig. 10.8b).

10.2.3 Conjunction of Molecules with SiNW: Chemical Functionalization Aspects

Azobenzene is one of the most frequently used light-switching molecules, which reveals simple cis-trans isomerization, exhibiting a big difference in structure and electric dipole moment between isomers induced by the irradiation of ultraviolet light (Fig. 10.9). Recently, the behavior and electrical properties of azobenzene monolayer on silicon surface have been investigated by several groups [25, 26].
Covalent bonds can be formed between specially functionalized azobenzene molecule and hydrogen-terminated silicon (Si–H) (Fig. 10.10). Authors demonstrate that the chemical bonds can be characterized by various surface analyzing methods such as contact angle, X-ray photoelectron spectroscopy (XPS), or attenuated total reflectance-Infrared (ATR-IR) spectroscopy measurement [25, 26]. Although a variety of investigations of molecular monolayer on silicon surface has been carried out, applications of Si nanowires have not been reported except for the photosensitive TiO$_2$ nanowires in conjunction with azobenzene [27].

For the case of porphyrin, molecules can be simply attached on silicon surface by both chemisorption and physisorption. Self-assembled monolayer (SAM) of porphyrin on silicon oxide (Fig. 10.11) has been studied by several groups [28–30] and is well investigated. In the case of established chemical binding between molecule and surface, electrons can migrate from porphyrin to silicon through covalent bond.

On the other hand, physisorption dominates as a result of the drop-casting, which is used in many applications for attaching porphyrin on silicon surface [31, 32]. When the porphyrin solution is dropped on silicon nanowires and the solvent is evaporated, porphyrin aggregates on nanowires and forms multilayer stack amor-phously. This can result in distinct interaction of the molecule with the surface, i.e.,

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Fig. 10.8  Interfacial energy-band diagram: a isolated silicon and organic molecules; b Junction, aligned Fermi level and interfacial dipole

Fig. 10.9  Simple isomerization of an azobenzene molecule
silicon nanowire, and leads to specific influence of the light-sensitive porphyrin layer on electric characteristic of SiNW-based FET devices.

### 10.2.4 Optoelectronic Switching with the Use of Nanowires

Optical switching of hybrid nanowire system depends on both switching property of molecule and optical property of nanowires. Photochromic molecules switch between two or more energy states, which leads to structural and electronic change.
such as geometry, dipole moment, HOMO–LUMO gap and redox potential on molecular level [21]. The individual molecular change affects macro-molecular conjugation such as wettability, charge, or conductivity. Process of charge generation by means of light irradiation is demonstrated in Fig. 10.12. During illumination, electron hole pairs are generated within organic molecules. Depending on surface states, negative or positive charge is induced at the interface by (1) the recombination processes of holes or electrons (2) [33]. Photo-generated electrons are directly injected into silicon (3) or are able to change the potential on nanowire surface.

Molecular-level switching induces charge in nanowires contacting with photochromic molecule. The conductivity of nanowires made of material with direct band gap can change by light irradiation, when the energy of photon is equal to or greater than the band gap of the material (e.g., TiO₂), as in the case of optoelectronic devices such as laser diode or LED. However, silicon does not absorb light efficiently due to its indirect band gap, so that switching of hybrid Si nanowire devices mainly reflects molecular characteristics.

Molecular dipole moment or potential change around nanowires acts as gating of nanowire FET and controls free electron or hole population in nanowires. On the other hands, molecules that release electrons with light absorption (e.g., porphyrin) exchange electrons with nanowires directly, as donor or acceptor. The difference of Fermi levels between molecules and nanowires dictates whether the molecules behave as donors or acceptors. Moreover, since the gate bias also shifts the Fermi level, gate voltage plays a key role for switching direction.

Naturally, the amplitude of switching current depends on molecular absorption spectrum, as shown in Fig. 10.13. This is because given a molecule, its HOMO–LUMO band gap determines the resonant wavelength. Thus, the absorption spectra are key factors for generating free electrons from the molecule.
10.2.5 Example: Applications of Nanowires-Based Hybrid Devices

10.2.5.1 Memory Applications

First hybrid devices have been fabricated and applied for memory cells, employing porphyrin complexes. The memory application has been demonstrated with the use of In$_2$O$_3$ nanowires grown with self-assembled monolayers of porphyrins. Co-chelated porphyrin showed memory effect by the redox states of metal ion in the porphyrin (Fig. 10.14). They provided the potential of porphyrin that can be used for memory devices by charge storing in molecule.

Another interesting application is hybrid nanogap FETs. In these devices, porphyrin is embedded into the nanofabricated gap in the oxide layer of conventional MOS structure (Fig. 10.15). Hybrid nanogap FETs can be utilized as nonvolatile memory cell by optical charging and electrical discharging of porphyrin. Under light irradiation, Porphyrin absorbs electrons from the silicon...
substrate and stores the electrons in the ring for writing. The gate voltage $V_g$ is used for the substrate to pull back the stored electron for erase.

**10.2.5.2 Hybrid CMOS Applications**

By integrating p- and n-type silicon nanowires, processed by top-down approach, hybrid CMOS has been fabricated, in which the properties of porphyrin is exploited for the incident light to control the device behavior (Fig. 10.16). The characteristics of porphyrin are undergoing changes depending on the types of nanowires in conjunction, and consequently, the conductance of silicon NW also changes in response to incident light. The switching direction is opposite between p- and n-type silicon nanowire FETs, so that the initial OFF state is switched to ON state, while the opposite switching occurs in n-type FETs upon irradiation.

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**Fig. 10.15**  
(a) Schematic diagram of the mechanisms of the optical program and electrical erase characteristics. The porphyrin charging process is based on photoinduced charge transfer (PCT), and the discharge process is based on electron–hole pair recombination.  
(b) Optical program and electrical erase characteristics of the porphyrin-embedded FET [32]
Once the devices are illuminated by visible light, nanowire surface charge affects the currents in n- and p-type FETs in opposite manner, and as a consequence, the hybrid CMOS acts as logic gate with optical inputs.

10.2.6 Future Prospects and Challenges

The applications of many photochromic molecules have yet to be demonstrated aside from porphyrin. Photochromic molecules can be utilized for biological application as well by attaching biomolecules at the end of photochromic molecule to be controlled by light illumination. Also, logic circuits driven by different wavelength of light is a possibility. However, the effective functionalization of hybrid device application is still a challenge. For practical applications, stable and reproducible functionalization is required. Also, analysis of surface state has not been carried out sufficiently and the electrical transfer mechanism in interface has yet to be examined clearly.
Combination of nanowire FETs with biological recognition elements boosts up
SiNWs to the level of biosensing devices (see conceptual image in Fig. 10.17),
enabling label-free detection of the analyte of interest in real time [4–7], and [35].
Crucial for all kinds of biosensors is the choice of specific receptor molecules and
their subsequent bioattachment to the functionalized sensor surface [36]. The
capture molecules are expected to bind the analyte with high affinity and speci-
ficity and to be stable under varying conditions. For a nanowire-based biosensing,
recognition elements should be small enough to enable a change of conductance of
the nanowire FET once the analyte is bound to its receptor. In this section,
functionalization of silicon nanowires will be described and on this basis, several
options for biorecognition elements will be presented.

10.3 Biodetection and Diagnostics

The aim of surface modification for biosensing is to place the biological receptor
molecules close to the transducer surface to achieve high sensitivity. The design of
each functionalization setup is crucial for the performance of the sensor. Oriented
immobilization or receptor densities may increase the signal whereas steric hin-
drance and unspecific adsorption should be avoided for high signal quality.
Electrochemical biosensors like silicon nanowire-based FETs require in addition a
short distance between the biorecognition event of receptor and target molecule
and the sensor surface [37]. These events are only detectable within the Debye
screening length which is defined by the ionic strength of a solution (approxima-
tely 3 nm in 10 mM ionic solution [18]). A low ionic strength increases the
Debye layer thickness; it is, however, competing with a reduced biosensing ability
as ions are needed to stabilize the structure formation of biomolecules. Otherwise,
the receptors might lose their specificity against the target.
The choice of the appropriate linker molecules for the surface functionalization strategy depends on both, the sensor surface and the possible functional groups for attachment of the receptor. In the case of Si nanowire devices, either SiO$_2$ or Si–H is present. Silicon nanowires are oxidized in ambient conditions resulting in a native oxide shell. Thermal oxidation leads to a more homogeneous surface which enhances reproducibility of the electrical properties. The oxide can only be removed for a short time by etching which results in hydrogen-terminated silicon nanowires. Before developing a functionalization scheme, it is necessary to decide for oxidized nanowire surfaces or hydrogen-terminated silicon. Biological receptors commonly expose free primary amines, carboxy, thiol, or aldehyde groups or can be synthesized with these functionalities. Consequently, the linker molecules should provide reactive groups able to bind the receptor in a reliable way.

### 10.3.1.1 Hydrogen Termination

After removing the oxide in strong acid (HF or NH$_4$F, see Fig. 10.18), the resulting hydrogen-terminated silicon is able to react with ω-alkenes. The C = C double bond at one chain end is catalyzed in UV light and covalently attaches to Si–H forming stable Si–C bonds. The long alkyl chains tend to form well-ordered self-assembled monolayers (SAM). By using carboxy-terminated molecules, receptors with functional primary amines can be easily immobilized on the modified nanowire surface. Bunimovich et al. demonstrated that DNA probes which were surface bound via electrostatic interaction to an amino-terminated oxide-free Si nanowire show a higher sensitivity for hybridization with the complementary strand than on an equally amino functionalized oxidized nanowire [38]. This advantage of hydrogen termination has to be counterbalanced with the etching step which is aggressive toward metallic materials on the chips.

### 10.3.1.2 Silanization

Organosilanes are the standard class of organic molecules for covalent functionalization of SiO$_2$. The core atom is a Si atom with four bonds, and the principal structure can be summarized in the formula $R_n SiX_{(4-n)}$, see Fig. 10.19. Whereas, $R$ is the organic terminal group usually chosen for further receptor attachment,
X represents a hydroxyl or hydrolyzable group consisting of -Cl or (m)ethanol. Hydroxylated silicon dioxide can react with these silanol groups forming stable siloxane bonds (Si–O–Si). Silane layers can be stabilized by postbaking which is said to lead to a cross-linking of unbound silanol side chains. The disadvantage is the possibility of polymerization in solution and undirected attachment of the silanes on the surface leading to inhomogeneous surface layers. This can be improved by replacing two X with nonhydrolyzable methyl groups. Another option is the electric field alignment of silanes which increase the device sensitivity, see Fig. 10.20.

To these, functionalized surface receptors can be attached covalently with different functional groups. As amino, carboxy, aldehyde, or thiol groups are the most abundant groups targets display, the surfaces are usually provided with the complementary chemical group: carboxy or aldehyde for amines and vice versa and thiolated surface for thiols. For some reactions, cross-linkers or activation steps are needed [42].

To give an example, Lee et al. used an aminosilane for modification of silicon dioxide, see Fig. 10.21 [43]. The cross-linker succinic anhydride attaches to the primary amine in a ring-opening reaction. After activation using zero-length cross-linkers, the functional amino group of the DNA strand can covalently bind to the surface carboxy group. The success of the modification steps can be analyzed with techniques like AFM or fluorescence, as Lee et al. published for DNA functionalyzed nanowires, see Fig. 10.21. Here, the height and roughness increase significantly due to the molecular layers.

**10.3.2 Role of Debye Screening Length**

As mentioned in the beginning of previous paragraph, the distance between the biorecognition event and nanowire is important for the FET sensitivity. By cutting the antibody and using only Fab fragments (the detecting region of antibody), the biorecognition takes place closer to the transducer surface and leads to an improved device performance, see Fig. 10.22. This effect can be enhanced by tuning the receptor density to a value of mean surface coverage (see Figure E, right scheme). Avoiding steric hindrance of the receptors, they can lay down within in
Fig. 10.20 Tuning the sensitivity of top-down fabricated SiNW FET by electric field alignment of the surface-bound organic molecules on a single NW device (left). Surface functionalization leads to irregular arrangement of organosilanes (middle: amino silane). Applying an electric field (right) leads to a higher degree of parallel arrangement which improves the device performance [41].

Fig. 10.21 (a) Functionalization scheme for a silicon nanowire with oxide shell for attachment of DNA as a capture layer. Topography analysis with AFM shows that after all immobilization steps, height and roughness of the sample have increased in (c) compared to the blank (b) [43].
sensitive region, higher densities force them to stand upright sticking out of the sensitive layer, see Fig. 10.22, left scheme. This technique also allows for higher ionic strength of the buffer solution which again stabilizes the biorecognition itself [18].

10.3.3 Noncovalent Binding of the Molecules

Noncovalent adsorption of molecules on SiNWs can also be employed for sensing purposes. Let us consider an example of lipid bilayers that have shown a great potential for multiple biotechnological applications. As an application SiNWs, they can be used to shield the nanowire surface (see Fig. 10.23, blue reference curve in the inset) and to prevent it from unspecific adsorption of the analyte molecules, like proteins. Due to the lipid mobility in bilayers, defects can heal easily increasing the device lifetime. By integrating pores in the membrane, it is possible to sense specific ions or molecules as the pores open upon their presence which results in a conductance change. Also pH changes initiate pore openings and can be detected [44]. Kinked nanowires have been coated with lipid bilayers to increase biocompatibility for measurements of single-cell potentials [45].

Fig. 10.22 Attachment of Fab fragments to an aldehyde surface (aminosilane linker and glutaraldehyde cross-linker). Biorecognition takes place above the sensitive layer for a high receptor density (left) whereas a mean density allows for molecule bending (right) [18]

Fig. 10.23 Scheme of lipid bilayer with pore protein on SiNW FET and pH sensitivity (upper graph) compared to pore-free bilayer (lower graph) which shows no change in the electrical behavior due to pH change from 6 to 9 as indicated [44]


10.3.4 Antibodies as Recognition Element

Antibodies are biological molecules that recognize very specifically a certain target. Antibodies consist of two heavy and two light chains. The \textit{Fab} domain is responsible for target recognition and each antibody is thus in principle able to bind two target molecules. It is the variable region that adapts to new pathogens and thus helps the immune system to fight the disease. The \textit{Fc} end of a class of antibodies is fixed on the contrary. There are two groups of antibodies—polyclonal and monoclonal, depending on their production process. Polyclonal antibodies are a pool of different antibodies that can detect an analyte whereas monoclonal antibodies are all identical. Antibodies are highly specific, but they are produced in animals and are relatively sensitive to varying environmental conditions which challenges the application in biosensing. In addition, the target variety is limited as antibodies have to occur naturally [46]. Several examples employing antibodies on Si nanowire-based FETs have been demonstrated so far showing their potential. Cancer markers like PSA (prostate specific antigen) could be detected down to a low concentration of 90 fg/ml with antibodies covalently attached to the SiO\textsubscript{2} surface via primary amines to the aldehyde terminated surface, see Fig. 10.24 [6].

\textbf{Fig. 10.24} Multiplexed detection of cancer markers on p-type SiNW array FETs by using different antibodies attached to the NWs (top scheme). PSA biorecognition leads to conductance changes with 90 fg/ml as a detection limit. The inset shows the conductance development with time [6].
Silicon nanowire FETs are able to detect single biorecognition events (single molecule sensing) as Patolsky et al. demonstrated and confirmed optically detecting influenza A virus using surface-attached antibodies as illustrated in Fig. 10.25 [5]. Another application was demonstrated by Mishra et al. for detection of bacterial toxin SEB (Staphylococcus aureus enterotoxin B) [47]. The antibodies were immobilized as a capture layer on the transistor via covalent bonding to the carboxy-terminated surface. By analyzing the impedance upon SEB recognition, the sensor response down to 1 fM of SEB was monitored.

10.3.5 Peptides as Recognition Element

10.3.5.1 Structure

In addition to antibodies, peptides can also represent specific capture molecules enabling for nanowire-based sensing of biochemical species. Oligopeptides consist of a small number of amino acids linked by peptide bonds (see Fig. 10.26). Due to their little size they are more stable than antibodies and can reveal high specificity that make them perfect recognition elements for biosensors at the nanoscale.

A size of the peptides allows the binding of the target molecules in close proximity to the nanowire surface, which potentially can increase the sensitivity of the biodetection. This argument together with the fact that such receptors can be artificially developed for a large variety of the targets represents a great advantage of using peptides for future biotechnology.

10.3.5.2 Peptides Development

Peptides for sensing can be chosen taking nature as a model [49]. Furthermore, peptides can be identified by a selection process similar to SELEX for aptamers against almost every imaginable target. This screening technology, called
biopanning, is based on phage display—the presentation of peptides on the surface of bacteriophage particles. Phage display was firstly introduced in 1985 by George P. Smith [50] and is now a widely expanding research field [51–53]. The marvelous idea behind is the linkage between the genotype and the phenotype of the phage: a foreign DNA with the information for the peptide is inserted into the genome of the phage and the peptide is displayed as a fusion to one of the coat proteins of the phage [52]. If the foreign DNA insert has got a randomized sequence, each phage will present a different peptide. Such a wide diversity of phages is called a phage display library and can be used to select those peptides by biopanning which are able to bind to a certain target molecule with high affinity and specificity. Peptides identified by phage display have become part of many biosensing applications [54] and would be a promising option for nanowire-based biosensors, too.

Fig. 10.26 Peptide structure. Each residue R represents an amino acid side chain [48]
Regarding nanowire-based sensing, peptides have been used as biorecognition elements for metal ion detection. Two different peptides—specific for ions Cu²⁺ and Pb²⁺—were immobilized on independently addressable clusters of silicon nanowires. The metal ions could be simultaneously detected and quantified. Although high amounts of additional Cu²⁺ ions influenced Pb²⁺ concentration measurements at low concentration, almost no interaction was observed for clinical relevant concentrations (see Fig. 10.27) [49].
10.3.6 DNA and PNA as Recognition Elements

10.3.6.1 Structure

Single-stranded DNA (ssDNA) can be detected by hybridization (see Fig. 10.28, right-hand side) using complementary single-stranded deoxyribonucleic acids (DNA) or artificial peptide nucleic acids (PNA). DNA is a polymer of nucleotides, which are made up of nucleobases and a negatively charged sugar phosphate backbone. In contrast to DNA, PNA has neutral backbone and consists of N-(2-aminoethyl)glycine units linked by peptide bonds (see Fig. 10.28, left-hand side) [55]. Compared to DNA, PNA is more stable and shows a higher affinity [5].

10.3.6.2 Applications in Nanowires Sensing

Li et al. immobilized ssDNA oligonucleotides on SiNWs and could show a strong conductance change when adding a 25 pM solution of complementary DNA, but no signal change for mismatch DNA. They could achieve a signal-to-noise ratio of 8 and 6 for p- and n-type wires, respectively [7]. SiNWs modified with PNA were used to detect wild-type DNA down to fM-level and to discriminate from mismatch DNA. Therefore, sensors were functionalized with PNA specific for a sequence from cystic fibrosis transmembrane receptor and it could be shown that DNA containing the ΔF508 mutation, an indicator for cystic fibrosis, gives a much smaller signal than wild-type DNA (Fig. 10.29) [56].

Fig. 10.29 Sensing of DNA using PNA as recognition element. Effect of 100 fM wild-type DNA (solid line) and 100 fm mutated DNA (dashed line) on SiNW conductance (a), Schematic binding of DNA to PNA on SiNW surface (b and c) [56]
Aptamers are a new class of receptors based on DNA and were first reported 1990 [57]. Aptamers are artificial ligands consisting of short oligonucleotides (single-stranded DNA or RNA) of a length of usually 15 up to less than 100 bases. Depending on their sequence, they possess a characteristic structure (quadruplex, pinhole or others). The structure is stabilized by ions, (see Fig. 10.30 for a thrombin binding aptamer). This enables the detection of target molecules ranging from small organic molecules (e.g., TNT [58]) up to large proteins like thrombin [59].

Compared to antibodies, the advantages are their low costs due to in vitro production and easy labeling with functional groups or fluorophores, the little batch-to-batch variations, their relatively high stability under nonphysiological conditions, and the larger variety of targets such as toxins [46]. However, developing a new aptamer is relatively complicated and requires multiple processing steps.

Aptamers are artificially designed receptors and have to be identified for each new target. This is carried out in a so-called SELEX process (systematic evolution of ligands by exponential enrichment) out of a library of ssDNA. Each oligonucleotide has the same length consisting of a randomized sequence of the predetermined number of bases. On both ends, primers with a fixed sequence are attached. They are used, e.g., for immobilizing the DNA. This library of typically

**Fig. 10.30** Model of aptamer–thrombin complex formation in the presence of sodium (a) and potassium (b) [60]
1,013–1,018 different combinations is incubated with the immobilized target, unbound DNA is washed away [46]. By changing the solution, bound molecules are eluted, followed by a further enrichment and are again incubated with the target. By repeating several rounds, one can possibly identify unique sequences for detection. Depending on the target characteristics, various SELEX procedures have been developed. In order to identify aptamers for small target molecules, Stoltenburg et al. developed a method called Capture-SELEX to attach the potential aptamer strand onto magnetic beads via hybridization with a short complementary strand [61]. If a very strong affinity occurs between the target and the aptamer, dehybridization takes place. By this, only excellent binders (=aptamer) are identified.

10.3.7.1 Applications in Nanowires Sensing

Since reported, aptamers have gained increasing interest for application in Si nanowire-based sensing due to their advantages for FET-based sensors. Because of the smaller size of aptamers compared to antibodies, biorecognition can take place closer to the transducer surface within the Debye layer [62]. Sensing of thrombin which plays a major role in the blood coagulation cascade was carried out with a 15-bases-long aptamer [63]. Thrombin was detected in model solutions (thrombin in buffer) as well as in blood samples (see Fig. 10.31). Devices with a control aptamer of a randomized sequence on the contrary did not show a signal change.

![Fig. 10.31](image.png)  
**Fig. 10.31** Real-time detection of thrombin in different samples with an aptamer-functionalized Si nanowire FET. The current changes due to biorecognition. The inset shows a control aptamer without conductance change after injection [43]
upon sample injection (see inset in Fig. 10.31). Tumor growth or the level of angiogenesis is often indicated by the presence and concentration of the vascular endothelial growth factor (VEGF) and thus its detection can be interesting in clinical applications. Lee et al. could measure VEGF down to the subnanomolar range with aptamer-functionalized Si nanowire FETs Lee [43].

10.4 Drug Delivery Applications

As it is reported in numerous publications and reviews, nanomaterials and in particular silicon nanowires can be considered not only as a backbone in diverse in vitro detection tests, but also as a highly selective drug carrier for in vivo applications [64–66]. Some of the prerequisites, which make nanowires to be superior for a number of applications in nanomedicine are related to their size properties, i.e., high surface area and elongated shape (high size aspect ratio), allowing easy penetration through the biological tissue [67, 68]. Furthermore, biochemical modification of the nanowires, usually covered by the shell of amorphous silica, is relatively easy [40]. Another important argument to explore 1D nanostructures for spying at the scale of single proteins or cellular machines is a simple size domain comparison of the nanowires and typical biomolecules. Because dimensions of the single molecules and nanoparticles nearly coincide, investigation of biological processes using nanotechnological tools become possible and can be performed without too much interference [69, 70].

Thus, after the decade of intense investigations of physical and chemical properties, nanowires entered the phase of application relevant research and even numerous commercial realizations [71]. Nowadays, the nanowires are in the scope of intense investigations for development of novel fluorescent biological labels, [72] drug and gene delivery, [73], tissue engineering, tumor destruction, to name just a few.

10.4.1 Construction of Nanowire-Based Biologically Active Drug Carrier

In order to use the nanowire as biologically active unit, i.e., vehicle for drug delivery, or contrast agent for in vivo imaging, it has to acquire necessary functionality. A biological or molecular coating, acting as bioorganic interface should be linked to the nanowires surface. Important role of the coating is to reduce the toxicity and to provide the biocompatibility of the nanowires with the surrounding environment. Some of the prominent examples of biological layers include monolayers of small molecules (e.g., fibronectin coating for better attachment of Fibroblasts), polymers like collagen [74, 75], DNA brushes, or antibodies.
Furthermore, the functionalized “nano vehicles” has to exhibit ability to be detected inside of the organism or testing tube using optical, electrical, electromagnetic, etc. techniques. Set of standard approaches used to construct the biologically active nanowires are schematically summarized in Fig. 10.32.

Silicon NW typically represents a core of the bioactive object. Since the core can carry important properties (e.g., luminescence or radio-frequency response), it should be covered by inert protective layer. In the case of silicon nanowires, amorphous native silicon oxide SiO_x represents a natural protection of the core. Alternatively, additional organic layers, consisting of, i.e., lipid shells can be formed around the nanowire to play a protective role [76]. In order to make nanowires suitable for biological tagging and labeling, linkers with diverse functional groups can be further immobilized at the surface of the covering shell. End group of the linkers is always aimed to attach various species, like antibodies, magnetic tags, fluorophores, etc.

10.4.2 Internalization of the Nanowires: In Vitro Tests

One of the strategies to deliver the relevant medications and contrast agents, or to probe and manipulate biological processes occurring inside the cells [67, 75], is internalization of the nanowires by the living cells. Internalization is defined by the process when the nanomaterials (i.e., nanoparticles, nanotubes, nanowires) are engulfed by the cells through their membrane [64, 77]. After numerous investigations in this field, it is assumed that so-called endocytosis (or phagocytosis for uptaking of the objects larger than 0.5 μm) describes most precisely the processes of the intracellular injection of the biochemical species and nanoparticles [78]. This process typically consists of few stages: (1) approach of the object to the lipid membrane; (2) formation of the lipid-based vesicle, wrapping the transported
species; (3) fusion of the vesicles inside of the cells; (4) unwrapping of the vesicle for sorting and targeting of the delivered species. To facilitate the internalization, surface properties of the nanowires must be predesigned and specifically functionalized to meet the requirements of cellular delivery and targeting (see Sect. 10.4.1).

In order to demonstrate the interfacing of the nanomaterials and living cells, let us consider an example of the mammalian cells such as mouse embryonic stem (mES) cells placed into direct contact with vertically grown silicon nanowires (Fig. 10.33). For these experiments, stem cells were cultured directly on a silicon wafer with as grown nanowires [67], as shown in Fig. 10.33a. SiNW array penetrated into the cell naturally, without applying any external force. It has been shown that nanowires internalization did not affect dramatically cellular metabolism, since the cells survived up to several days on the nanowire substrates. Confocal microscopy was used to visualize the cells with nanowires penetrated inside (Fig. 10.33b).

Whereas first studies have demonstrated the possibility of vertical nanowires to penetrate spontaneously cells’ membrane, further work was dedicated to generalize the use of silicon nanowires and to represent nanowires as a universal platform to deliver a large variety of the biological species, which can affect cell activity [79]. In particular, it is known that large variety of the complex cellular processes can be probed and analyzed, by integrating surface-modified SiNWs, delivering diverse range of biomolecules into living cells. To achieve this rich output, an approach, introduced in Fig. 10.33, is further developed to internalize a broad range of bioeffectors, i.e., DNA, RNA, peptides, and proteins (see Sect. 10.3) into almost any cell type. This ability is summarized in Fig. 10.34.

Note that silicon nanowires can be covered by aminosilane groups, which provide noncovalent binding of the molecules to the NWs. Thus, molecules can be released from the wires surface, once internalization happened [64, 66, 67, 79]. Thus, in vitro internalization of silicon nanowires carrying biomolecules might be

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**Fig. 10.33** Penetration of the silicon nanowires inside of the stem cells mES. a incubation of the stem cells on the silicon substrate in order to internalize nanowires; b Confocal microscopy image to visualize mES with penetrated SiNWs [67]
considered as an excellent tool to assist in discovery new aspects of fundamental
cell behaviors, such as motility, proliferation and differentiation, adhesion, etc.

10.4.3 Nanowires-Based Drug Delivery: In Vivo Tests

After the number of successful in vitro tests where the uptake of the silicon
nanowires by numerous cell types were studied, the research of SiNW cells
conjugates reached the phase of in vivo assays. Traditionally, one of the most
common areas where the nanomaterials meet biotechnology is closely related to
anticancer therapy [66, 73]. The intense investigation of the drug delivery pro-
cesses is motivated by certain deficiencies of the traditional treatment. Among
them are the facts that (1) only a small amount of conventionally delivered anti-
cancer drug can penetrate into tumors; (2) strong distribution of drugs into non-
target tissues; (3) short circulation time in the blood. Use of the nanomaterials for
novel diseases (i.e., cancer) treatment is considered as a new paradigm, which
enables the dramatic increase in the drug concentration inside of target tissue due
to its high loading capacity.

In order to demonstrate the capability of the silicon nanowires to internalize and
deliver concentrations of the drugs, sufficient to inhibit growth of the tumor, let us
focus on in vivo therapeutic examinations of the mice bearing epidermoid carcino-
noma tumor (KB) on their back [66]. For these purposes, the anticancer antibiotic
doxorubicin (DOX) is associated with SiNWs by physisorption. An ultrahigh drug-
loading capacity of 20800 mg/g has been shown for these particular experiments.
A summary of the effect of SINW-DOX complexes on mice KB cells is depicted in
Fig. 10.35.
Mice population with KB tumors was divided into four groups, treated with (a) physiological saline, (b) pure SiNWs, (c) free DOX, and (d) SiNW-DOX complexes. In the case of doxorubicine therapy (c and d), two concentrations of 5 and 25 μg/kg were administered, respectively. Afterward, the mouse autofluorescence analysis was performed to estimate the efficacy of the treatment. Obviously, SiNW-DOX complexes revealed high killing rate of the tumor on the one hand, and extremely longtime accumulation of the drug in the tumor region.

10.5 Challenges and Perspectives

SiNW-based sensors hold up the potential as efficient and powerful vehicles for biodetection and biomedical diagnostics. These sensor devices offer the capability of high-sensitivity sensing and easy signal readout in real time without time- and money-consuming labeling steps. However, the detection sensitivity depends on the ionic strength of the sample, and therefore, high ionic strength solutions like blood as a desalting step is advisable. Additional challenges consist of checking the reproducibility of biosensing results for a given target molecule and producing the market-ready biosensing devices. A vision would be to implement parallel detection of a huge number of different analytes to get a high-throughput screening method, comparable and even better than DNA or protein microarrays, but on a biosensing level.

SiNWs conjugates with organic and biomolecules represent excellent platform to study fundamental behaviors of the cells such as adhesion or proliferation. From the point of view of practical applications, i.e., drug delivery, there are ongoing research on specificity, toxicity, and biodegradability of the nanowires in the living organism. Nevertheless, nanowires are considered as very promising candidates.
for the future therapy, since they are able to provide high drug-load capacity and targeted transport of the medicines.

So in future, it might be possible to simultaneously screen hundreds of biomarkers for medical or environmental purposes, and using nanowires with specific bioactive layers for diseases treatment, making thereby “lab on a wire” a reality.

References


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