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REVIEW PAPER

Field effect transistor nanobiosensors: State-of-the-art and key challenges as point of care testing devices

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ABSTRACT

The existing health care systems focus on treating diseases rather than preventing them. Patients are generally not tested unless physiological symptoms are appeared. When they do get tested, the results often take several days and can be inconclusive if the disease is at an early stage. In order to facilitate the diagnostics process and make tests more readily available for patients, the concept of "point of care testing" (POCT) has been brought up and developed in recent years. Field effect transistors (FET) using nanomaterial as a kind of biosensors have shown great characteristics for detection of a wide range of biomolecules due to their label-free, real time and ultrasensitive properties. In this paper, first of all, the working principles of such devices and recent developments in fabrication methods and surface functionalization are stated, and then some current research trends in field-effect transistor nanobiosensors are highlighted. Eventually key advantages and challenges of FET-based nanobiosensors as POCT devices are discussed as well.

Keywords: *Field effect transistor, FET-based nanobiosensor, Nanobiosensor, POCT*

INTRODUCTION

Sensor technology has been an important part of many sectors of society ranging from agricultural and energy to transportation security and medicine. The explosion of nanotechnology within the last twenty years has pushed the boundary of response times, detection limits, sensitivity, portability and etc. for sensor technology, particularly for chemical and biological sensors. This is partly due to the fact which nanostructures that have at least one dimension in the range of 1 to 100 nm have comparable sizes as many of the chemical and biological species of interest, and are thus better for probing the molecules. Another important feature of the nanostructures is their large surface to volume ratio that allows their material properties to be strongly affected by their environment. In the past few decades, many kinds of biosensors have been developed using different nanomaterials as a sensing element (cantilevers, quantum dots, nanotubes, NWs, nanobelts, nanogaps, and nanoscale films) [1-4]. Some of these sensing devices, such as ones based on cantilevers and quantum dots, are highly specific, ultrasensitive with short response times. But in order to understand surface-binding interaction, these devices need to use optical components to produce a readable signal. The need of detection optics is expected to increase the cost of operation for such a device significantly. Unlike this, sensors designed to operate like FET can directly translate the analyte–surface interaction into a readable signal, without the need of elaboration of optical components. These devices in order to produce the signal output benefit from the electronic properties such as conductance of the sensing element. Field effect transistors (FET) using nanomaterial as a kind of biosensors have showed great characteristics for detection of a wide range of biomolecules due to their label-free, highly specific, real time and ultrasensitive properties that promise to revolutionize bioanalytical research [5-8].

Field-effect transistor (FET) nanobiosensors

A common FET nano-biosensor includes the structure of a three-electrode transistor. The drain and source electrodes are connected by the semiconductor channel as well as the gate electrode modulates conductance of the channel [9]. The structure of an FET sensor is illustrated in (Fig. 1).

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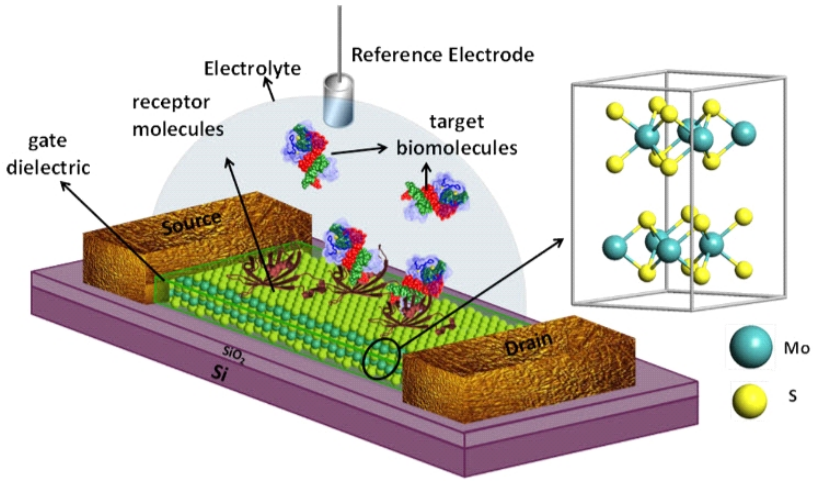

Fig. 1. Typical 2D MoS2-based FET biosensor device. For biosensing, the dielectric layer covering the MoS2 channel is functionalized with receptors for specifically capturing the target biomolecules. The thickness of the MoS2 flake used is 5 nm. Reprinted and/or adapted with permission from [17] (Copyright © 2014, American Chemical Society).

Channel as a "sensing" component of the FET nanosensor device is made of 1D or 2D nanomaterials [10]. In order to identify a unique analyte via FET nanosensors, a specific recognition group which is also called a probe, ligand, or receptor is employed. This recognition group is anchored to the surface of the semiconductor channel. It's clear that for providing a high degree of both specificity and affinity in FET biosensors, each specific receptor should be employed to realize its target analyte. Then, according to the type of receptor used for the target molecule diagnosis, FET biosensors can be classified into several groups such as DNA-modified FETs, immunologically modified FETs, enzyme-modified FETs and cell-based FETs.

The semiconductor used as a channel has a consistent conductance and is specified by main carrier density in the nanomaterials which can be determined from the source-drain current in device, so carrier density is proportional to the conductance of the channel (electrons for an n-type semiconductor or holes for a p-type semiconductor). Therefore any change in the conductance of the channel change generates a change in the source-drain current.An electric field is generated on the surface when a charged molecule (analyte) binds to a receptor anchored on the nanomaterial, and this connection exerts an effect outside and inside of the channel [11]. For instance, when an analyte molecule such as DNA with a negative charge binds to the p-type channel, due to the charge of analyte is opposite to the main carriers in the channel, the charge carriers will accumulate under the bound analyte, which causes a buildup of hole carriers and consequently an increase in conductivity of device will be displayed. This mechanism is shown in Route A in (Fig. 2). On the other hand if a positively charged molecule, such as a protein binds to the p-type channel, a depletion of main carriers beneath the bound analyte in the device channel and a decrease in conductivity will occur. This case is illustrated in Route B in (Fig. 2).The source-drain current of the channel is monitored against time. In route A, when a negatively charged target binds to the receptor anchored on the nanomaterial, the charge carriers will accumulate under the bound analyte that causes an increase in the device conductivity and source-drain current. In route B, the binding of a positively charged target leads to depletion of charge carriers beneath of the bound analyte, causes a decrease in conductivity and source-drain current [9].The mechanism of the conduction changing during molecular binding is also a debated topic [13-16]. According to the ideal transistor linear (region often used for biosensing) current equation is:

$$I_{DS} = e\mu\varepsilon\varepsilon_r \frac{A}{d}\frac{V_{DS}}{L}(V_{GS} - V_T)$$

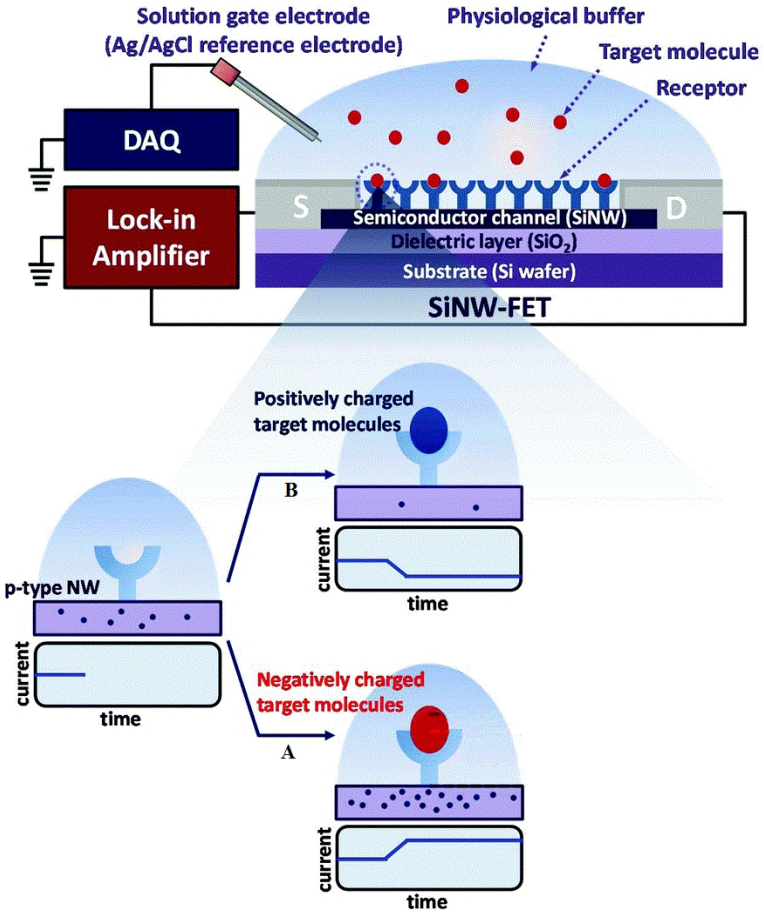

Fig. 2. Mechanism to modulate the conductance of a p-type nanomaterial-based FET (holes as the main charge carriers). Reprinted and/or adapted with permission from [12] (Copyright © 2013, Royal Society of Chemistry)

While the transistor dimensions (A, d, and L) and the drain voltage (V_{DS}) are constant, a change in conduction current (I_{DS}) can be caused by either a change in mobility (μ), a change in capacitance due to the difference in the dielectric constant (ε_r) of the sensing environment versus the binding molecule, or a gating effect (V_{GS}) caused by charges from the binding molecule. These three situations are illustrated in (Fig. 3) by comparing the $I_d - V_{1g}$ curves of an ambipolar FET device before and after protein binding. (Fig. 3(a)) shows that a decrease in the slope of the $I_d - V_{1g}$ curve after protein binding also decrease the Ids at fixed V_{1g}.

A change in I_{AS} due to the slope indicates a reduction in mobility and transconductance inside the channel, possibly due to an uneven electrostatic field distribution caused by random binding with charged biomolecules. In (Fig. 3.(b)) the gate bias is shown to be less effective at inducing I_{AS}.

The current reduction in this case can be attributed to a reduced gate capacitance made by the low permittivity of the bound biomolecule. Finally, (Fig. 3(c)) shows an Ids change because of electrostatic gating of the FET channel by charged target biomolecules. This type of change causes a threshold voltage (V_T) shift like in the (Fig. 3).

Nanomaterial and device fabrication

FET biosensors with different abilities and characteristics have been developed for biological applications. We categorized them into immunologically functionalized FETs, cell-based FETs, and enzyme-modified FETs. The main difference between various kinds of FET biosensors is created by the channel and interface material. A wide range of nanomaterials, such as molybdenum disulfide [17], graphene [18], carbon nano tubes [19], magnetic nanoparticles [20], indium oxide [21], titanium dioxide [22], gallium nitride [23], zinc oxide [24] and silicon NW [6] as a channel material of FET biosensors have been investigated by various research groups.

One-dimensional (1D) nanomaterial due to its small diameter, high aspect ratio and large surface-to-volume ratio has been used for nanotechnology applications in medical devices, electronics and sensors. Processes of preparing nanowire (NW) for FET-based sensors are classified into two major techniques: ''top-down'' and ''bottom-up''.

The top-down processes take place using lithographic processes, thermal evaporation, ion implantation, reactive ion etching (RIE) and electron-beam lithography, defines NW [25, 9]. The bottom-up methods carried out through growth of NWs, using chemical vapor deposition (CVD)[26], hydrothermal/solvothermal synthesis [27] and template deposition [28], among which CVD has a better control over the dimensions of the nanowires (NWs) and gives a better yield. Thus, vapor deposition (CVD) has become the most common method for synthesizing metal oxide NWs, silicon NWs and also carbon nanotubes. Several methods such as electric-field-directed assembly, flow-assisted alignment, polydimethylsiloxane (PDMS) transfer method, Langmuir-Blodgett technique, roll-to-roll printing assembly, smearing-transfer method and bubble-blown technique have been used for NW assembly and electrode fabrication [29, 9].

Once the nanomaterials have been prepared, the source, drain, and gate electrodes are deposited to complete the structure of the FET.

Most of the research groups have employed Si substrate as the back gate electrode. In the case of bottom-up NWs, the NWs are randomly dispersed on the substrate and metal source and drain electrodes are deposited on the insulating layer (for example SiO2 of 500 nm) on top of the NWs to define the channel length and width of the FET (Fig. 4(b)).

It has been reported that the device dimensionality directly affects the response time [30] and the sensitivity [31] of sensors. A common channel length is on the order of 2-10 μm.

In the case of top-down nanowires with leads there are patterns with uniform width and length at designated locations and metal electrodes which are deposited to create electrical connections (Fig. 4(b)).

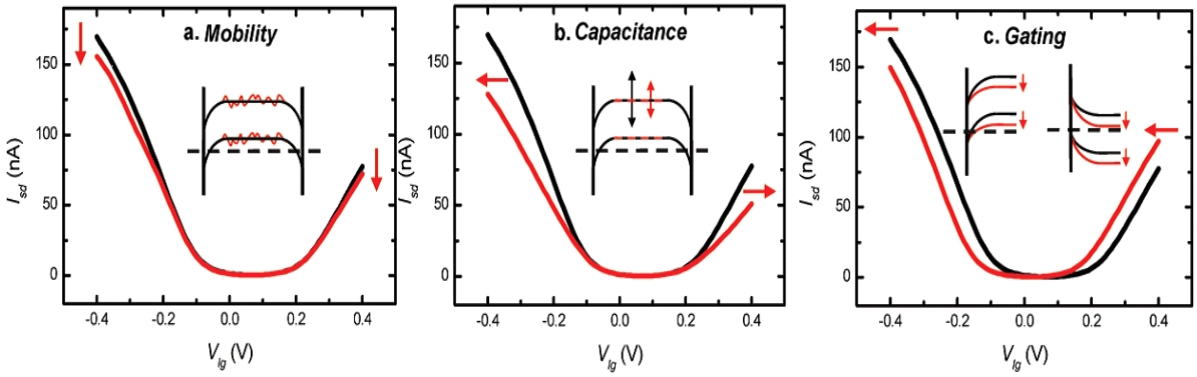

Fig. 3. Simulation of drain current (I_{as}) against gate voltage (V_{1g}) curves for before (black) and after (red) protein attachment on an ambipolar carbon nanotube FET sensor due to (a) mobility change, (b) dielectric change, and (c) gate bias. Reprinted and/or adapted with permission from [13] (Copyright © 2008, American Chemical Society)

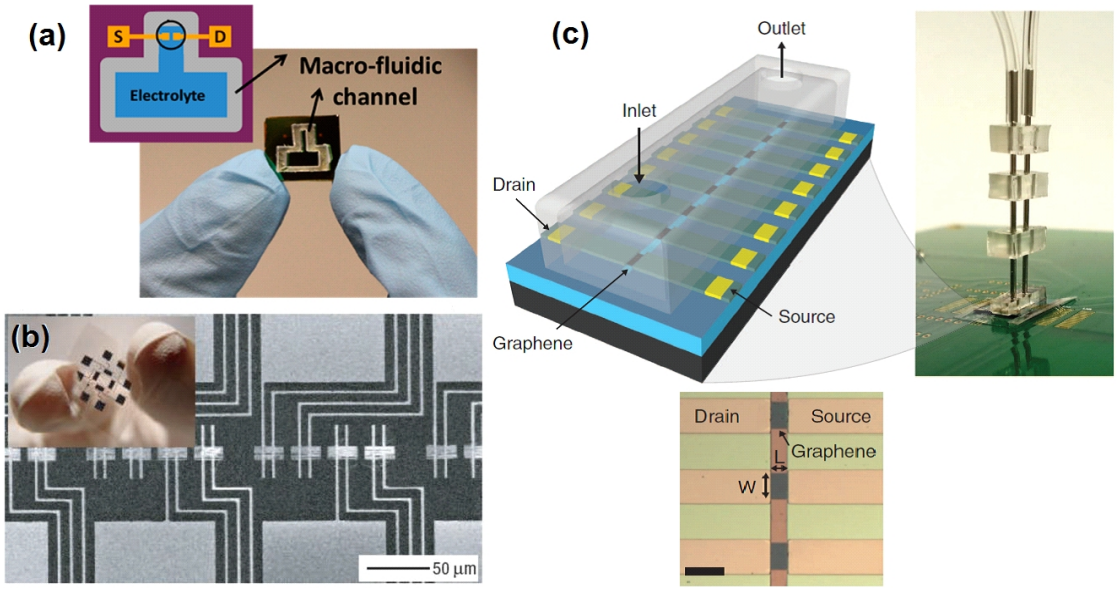

Fig. 4. Images of FETs nanobiosensor. (a) Image and schematic diagram (inset figure) of the chip with MoS2-based PH sensor device and microfluidic channel for containing the electrolyte. (b) Scanning Electron Microscope image of SiNW-based sensor platform and Digital photograph of the flexible sensor chip. Each device (horizontal strip) is contacted by two Ti electrodes (oriented vertically) that extend to larger pads (top and bottom image edges). This flexible sensor is used to accurately monitor NO2 concentrations in air. (c) Illustration and image of an 8-graphene-electrode/FET array with a microfluidic channel on top. This entire device sits on a printed circuit board. Chemical vapor deposition graphene is especially suited for multiplexed electronic DNA array applications. (a) Reprinted and/or adapted with permission from [17] (Copyright © 2014, American Chemical Society) and (b)-(c) from [97, 98] (Copyright © 2007, Nature Publishing Group) respectively

The bottom-up fabrication utilizes the random assembly of the nanomaterials, mostly one-dimensional (1D) nanomaterials, and electrodes are patterned on top of that. Interdigitated electrodes are used in order to increase the chance to bridge two electrodes with the nanomaterials. The top-down fabrication controls the position and the dimensions of the nanomaterials used in FET channel and electrodes are defined based on the location of the channel materials. The difference in controllability between two fabrication techniques results in the significant difference in device yields and uniformity.

Ishikawa et al. [32] stated, because of the randomness of nanomaterials position for bottom-up fabrication, a wafer scale device yield can only get as high as 74% in their In2O3 NW FETs fabrication, with noticeable device-to-device variation. On the other hand, the top-down fabrication can achieve almost 100% wafer scale device yield with minimal device-to-device variation, thanks to the good controllability over not only the channel position but also the precise dimensions [21].

In recent years, 1D FETs using polymeric nanowires including deuterated polymer (DP), polyaniline (PANI), polycarbonate (PC), polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), polystyrene (PS), polymethyl methacry-late (PMMA) and polyacrylamide (PAM) have been developed. In compare to the physical or chemical nanolithography techniques used for semiconductor wires, fabrication of polymeric nanowires through one-step drawing technology and electro spinning method provide more customizable functionalization and cheaper fabrication that can be widely applied and promoted, but polymeric nanowires show inferior electrical characteristics [33-36].

While the bottom-up fabrication methods for 1D structures encounter severe integrability issues [37, 38] the top-down methods face slow production rate

and high cost [38] so its forming limitation in the usability of these structures. On the other hand, the materials with 2D structure such as CNT, MoS2 and graphene, due to their atomically thin structures can provide excellent electrostatics and also because of possess planar nature they are suitable to large-scale fabrication and integrated device processing [37, 39, 17]. The micromechanical exfoliation technique has been used to obtain MoS2 flakes (Fig. 4(a)), Graphene sheets (Fig. 4(c)) and various 2D materials [17].

Nanobiosensors with good performance should possess the following qualities, especially if these devices are being used for bioanalytical applications:

1.Outstanding selectivity or specificity
2.High sensitivity and reproducibility of results
3.Short settling time (time necessity to capture the analyte)
4.Fast recovering time (time to regenerate a device after a measurement)

These qualities are affected by several followed parameters, which are related to fabrication techniques and experimental conditions:

I. Channel nanomaterial dimensions
II.Device geometries
III.Surface modification techniques
IV.Delivery system
V.Active measurement parameters
VI.Gating the device

Current research trends in field-effect transistor nanobiosensors

Massive amount of researches have been devoted to field-effect transistor nanobiosensors over the past decade. Efforts have been made to produce ultrahigh sensitivity, great specificity and minimal sample preparation process in order to apply such nanobiosensors for Point-Of-Care (POC) settings. Currently there are several popular research directions in this field to facilitate the widespread adoption of such technology.

Device structure engineering

Scientists and engineers are trying to create novel device structure to achieve higher sensitivity and different functionality for the FET nanobiosensors. Traditionally, an FET consists of three electrodes and one semiconducting channel. Ahn, et al., has added a secondary gate electrode to improve the sensitivity of their FET nanobiosensors [40]. By means of the secondary gate, it is easy to control the carrier conduction paths, which critically affect the device parameters such as the subthreshold slope, threshold voltage, and drain current. It was experimentally observed by antibody-antigen interaction and theoretically supported by the commercialized simulator that the nanowire structure with the double gate showed improved sensitivity in compare to that with a conventional single gate.

Multiplex sensing

Due to the complexity of biological systems, especially the human body, a single biomarker is not effective enough by itself for accurate diagnosis. Medical diagnosis using single biomarker probably occurs in a high possibility of false negative and false positive. Recent research shows that combination of multiple biomarkers generates improved accuracy compared to single biomarker [41, 42]. This fact brings up the importance of multiplexing assay of biomarkers. An ideal biosensing technology should be capable for simultaneous detection of a combination of biomarkers. In construct to sensor arrays for multiplexed biosensing, the sensors must be selectively functionalized with different capturing probes against their designated analytes. Efforts have been made to achieve the selective functionalization of nanomaterial-based devices, by using microfluidic chips, microspotting techniques [43, 44] and electroactive monolayers [45, 46].

In the case of multiplexing for NW-FET, Liber's group has proposed an appropriate simultaneous test for three cancer markers in desalted serum samples with a detection of 0.9 pg/mL [44]. For each of the targets, specified monoclonal antibodies were figured out through NW-FETs. Microfluidic channels delivered sample solutions and during exposure to each of the targets the signal monitored in real time from each FET. Compared to the microspotting technique, the employment of electroactive monolayers has a notable benefit because this method is just restricted by the ability to address the individual sensors electronically [46]. In this method, the vital point is to create a bifunctional molecule that possesses a nanomaterial-anchoring group and an electroactive moiety on its two ends.

The molecule is chemically inert. When the molecule covalently links to the nanomaterial of the channel such as NW, the electroactive moiety of that

reacts with the desired capture probe, therefore the molecule can be activated by employing an external voltage to electrodes [47].

Physiological samples

With today's nanosensors, researchers claim that they are able to detect proteins and DNAs down to femtomolar or even attomolar range with good selectivity [44, 48, 49, 96]. However, these detections are performed in purified buffers with very low ionic strengths. When it comes to clinical diagnosis, the sensitivity and selectivity of a biosensor will be significantly suppressed due to the complexity of the sample composition. Efforts have been made to address this problem by sample purifications and novel surface modification approaches.

Mark Reed, et al., has reported biomarker detection from whole blood samples purified by a microfluidic purification chip (MPC) [50]. The biomarkers spiked in a whole blood sample were captured by an antibody-modified MPC and antibody/antigen complexes were released into 0.01X PBS buffer. The complex solution was then delivered to Si NW-based sensors functionalized with a secondary antibody to perform sensing. This research evaluates the use of label-free nano-biosensors with physiological solutions for the first time. In order to overcome the complication caused by physiological samples, Chang et al. developed a faster approach without requiring extra process for device fabrication. They blocked the signal induced by nonspecific binding via passivating the In2O3 NW surface with an amphipathic polymer, tween-20, once doing active measurement in whole blood [51]. As they revealed, the detection range of amphipathic polymer passivated FET biosensors for biomarkers in whole blood which is similar to the detection range in purified buffer solutions for the same analyte and at the same ionic strength. As well as, this in the complex media, this method shows minimal decrease in device performance.

Surface functionalization of field effect transistor for nanobiosensors development

Abilities of a FET nanosensor in recognition toward a desired analyte highly depend on the surface properties, thus the sensing element (semiconductor nanomaterial) needs to be modified otherwise FET will not have the favorable molecular recognition abilities. This selectivity is typically achieved by anchoring a specific recognition group to the surface of nanomaterials. A bifunctional linker molecule with two chemically different termini is used to help anchor the receptor molecules to the nanomaterial surface. In this section, I focused on the surface functionalization of metal oxide and Si materials.

Surface functionalization of metal oxide semiconductor

Metal oxide surface can be functionalized with a linker molecule that bears a functional group capable of forming a nonhydrolizable conjugate, such as phosphonate or siloxide. Phosphonic acids are found to bind strongly on the surface of In2O3 and ITO [52, 53]. Silane molecules have been applied to functionalize ZnO and Fe3O4 surfaces [54, 55]. Also carboxylic acids, especially fatty acids, have been used to functionalize TiO2 nanoparticle surface [56].The optimum linker molecule was found to be a phosphonate derivative, like 3-phosphonopropanoic acid [57]. This phosphonate spontaneously self assembles on the nanowires from aqueous solutions or polar solvents. A major feature of the attachment of a phosphonate group on a metal oxide surface is that the anchorage can be mono-, bi-, or tridentate (Fig. 5). For example, a recent investigation of the binding of (11-hydroxyundecyl) phosphonic acid or (12-carboxy-dodecyl)phosphonic acid on a SnO2 surface by solid state [53] P NMR showed a bi- and tridentate attachment of phosphonate ligands [58]. The multidentate attachment is another stabilizing factor for the modified nanoparticles [59, 60]. In the case of the bifunctional (12-carboxy-dodecyl) phosphonic acid, it is interesting to note that the phosphonate group and not the carboxylate group was bonded to the stannia surface, which proves the phophonate group is more favored to form the covalent bond compared with the carboxylate group.

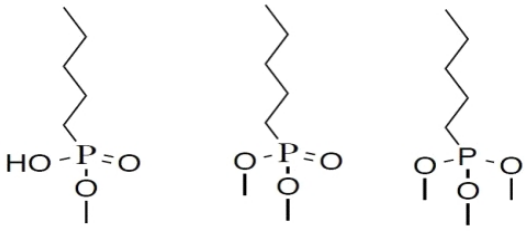

Fig. 5. Mono-, bi-, or tridentate anchorage of a phosphonate ligand on a metal oxide surface

Surface functionalization of Si materials

Si surface forms a thin layer (approximately 2 nm) of SiO2 because of the oxidation process when exposing the material in the air. The surface functionalization schemes are dependent whether the surface oxide layer is removed or not. Alkoxysilane derivatives, such as 3-(trimethoxysilyl) propyl aldehyde, 3- aminopropyltriethoxysilane and 3-aminopropyldimethylethoxysilane are the most widely used linkers for the Si surface with the native oxide layer [44, 15, 61, 62]. The Si-methoxide or Si-ethoxide reacts with the surface OH group, anchoring the linker molecule to the silicon oxide surface and creating a monolayer terminated with aldehyde or amine groups. These groups can then react with amine or carboxylic acid groups that are commonly present in biological capture probes. As for Si surfaces without the native oxide layer, two methods have been employed to functionalize the surface for further bioconjugation. Several research groups use UV light to rapidly photo dissociate the Si-H bond to engender radical species on the Si surface (Fig. 6). This action results in forming stable Si-C bonds at the Si surface through reaction between these radicals and terminal olefin groups on linker molecules [63, 64, 65]. The linker molecules usually carry a protected amine terminal, which can be used to attach biological probes after deprotection. The other method, developed by Nathan Lewis, uses a two-step chlorination/alkylation reaction to form Si-C bond on the surface [66, 67]. The Si- H surface is first chlorinated to form Si-Cl bond and then the surface was treated by an allyl Grignard. The resulted allyl surface can be used for further bioconjugation [68].

Current research trends in surface functionalization of semiconductor materials

Scientists are trying to engineer the surface of materials with reactions that are normally carried out in liquid phase. Organic synthesis has endowed researchers with a significant amount of reactions to work with. Surface chemists start to involve some of the "star" reactions that are highly yielding for surface functionalization.

Click chemistry

The click chemistry approach in various branches of materials science and polymer chemistry, has achieved notable attention during the recent years, [69, 70] since Sharpless introduced it in 2001 [71]. The concept addresses several criteria. The reaction has to be modular and wide in scope, provides furthermore very high yields, generates inoffensive byproducts, is stereospecific, also can be carried out using mild reaction situations as well as with easily available starting materials [71]. The purification can be ideally gained through nonchromatographic ways. The Huisgen 1,3-dipolar cycloaddition of organic azides and acetylenes is the most perfect click reaction that is presented up to date [72]. Therefore, it results in forming of a composition of 1,4- and 1,5-disubstituted 1,2,3-triazole systems. Reaction between the copper catalyzed coupling of azides and terminal acetylenes is the other type of this approach that results in forming of the 1,4-disubstituted triazole [73, 74]. The click chemistry can satisfy the requirements of chemical reactions performed on surfaces as well. This is proved by a sizable number of investigations. Various research groups have evaluated using of click chemistry for functional groups into the monolayer system on various substrates, e.g. gold, silicon and glass [75-77]. Fig. 7(a) and (b) are two synthetic preparation procedures that are applied to introduce 1,2,3-triazole moieties into the monolayer. Fig. 7(a) illustrates using of azide terminated substrates for the coupling with functional acetylenes and Fig. 7(b) shows the generation of surfaces with terminal acetylene moieties.

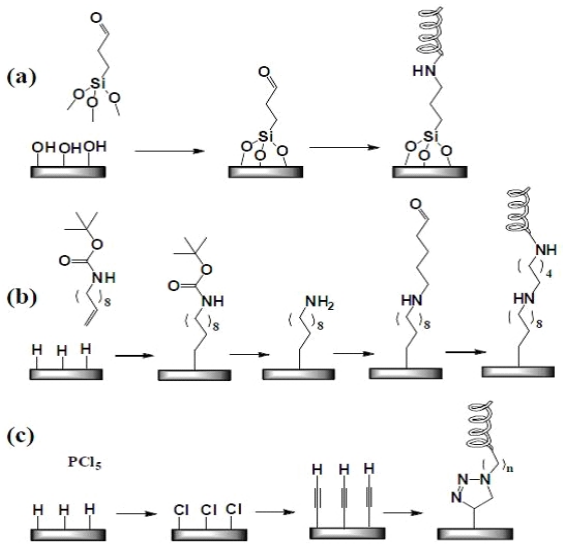

Fig. 6. Chemical pathways used to anchor biological molecules to different nanomaterial surfaces. (a) Si surface coated with native oxide. (b) H-terminated Si surface functionalized with an Olefin. (c) H-terminated Si surface functionalized with the chlorination/alkylation method

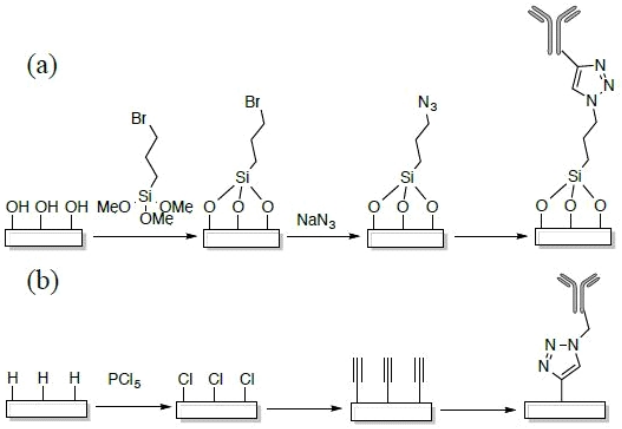

Fig. 7. Schematic representation of two pathways for surface click chemistry: (a) azide terminated surface and (b) acetylene terminated surface

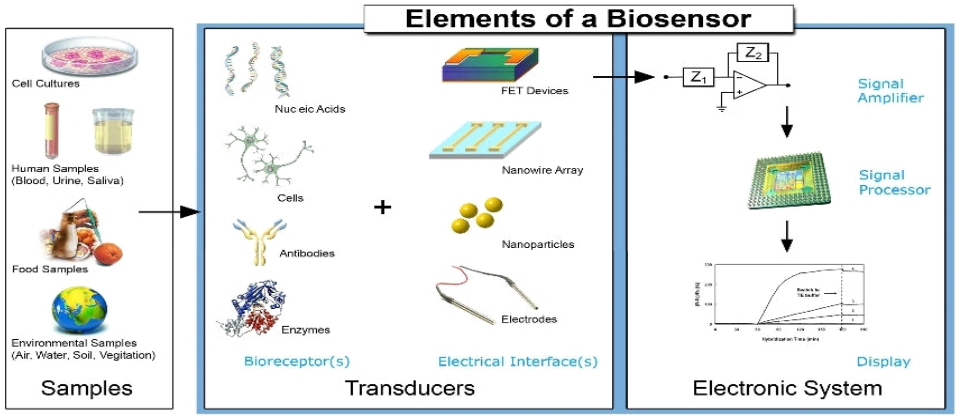

Fig. 8. POCT device that consists of a bio-recognition layer on a transducer attached to an analytical output. Reprinted and/or adapted with permission from [89] (Copyright © 2008, by MDPI)

Current research trends commercialized POCT devices

The most successful POCT device on the market now is the glucose meter. It has been developed for more than 50 years and was commercialized in the 1980s. The current glucose meter delivers accurate, rapid test result with minimum sample volume and simple procedures. However, glucose meter only detects one substrate and thus lacks the versatility for a broader range of other substrates. Since it is a perfect platform for accurate and rapid test, research has been around applying such a platform for a more general spectrum of biomarkers. Xiang and Lu combined the glucose meter with a separate DNA sensor and successfully extended the glucose meter to detect a variety of target molecules, with decent detection limits and dynamic ranges [90]. Another POCT platform is the lateral-flow testing strip. The widely used pregnancy test strip is based on such a platform. Currently on the market, the later-flow strips are developed for a large variety of biomarkers. Although this platform is able to deliver rapid qualitative test results, the relatively high detection limit and false positive rate make the conventional lab test still a must for a more confirmative result. Moreover, a much more complicated technology is required to conjugate with the lateral-flow assay in order to obtain quantitative test results [91]. Examples are to use spectroscopy to read the intensity of the sample colored line on the strip, which is similar to the ELISA process.

TheranosTM, a bay area-based biotech company, starts to provide services to detect a large variety of analytes with only a finger prick of blood. The company is currently pairing with doctors to deliver test results for certain analytes within hours, instead of days for conventional test turn-around time. The analytes cover a large number of protein biomarkers, different chemical elements, small molecules and blood cells. More importantly, the company has started to work with Walgreens to bring the testing service in Walgreens store for a more convenient experience for patients. Database will be established for a certain patient to monitor one or several specific biomarkers chronically, providing physicians a closer track of the health condition of the patient [92]. The technology of the company, though not disclosed on their website, is mainly optical sensing and ELISA-type sensing technology based on several of their issued patents [93].

They have engineered the sample delivery system and sensing assembly for faster testing process and smaller sample volume [95]. So far, TheranosTM is the most successful company to provide POCT services on the market and with the establishment of their TheranosTM Wellness Center in Walgreens, this service will surely become more prevalent and the development of POCT devices will be even more demanding.

Advantages and challenges of FET-based nanobiosensors as POCT devices

POCT devices require rapid and accurate test results from minimum sample volume and easy sample handling without well-trained personnel. FET is potentially a favorable platform to develop reliable POCT devices. The fast response of the electrical signal induced by the external electrical field on the transistor is instant, which is very important for repaid sensing result delivery. Furthermore, the electrical signal can be easily integrated with other electronics components for signal processing and readout.

Similar to the glucose meter, the use of electrical signal will enhance the portability for the application of the FETs as POCT devices.

FET-based nanobiosensors use nanomaterials for the semiconductor channel. With the help of nanoscale size of the channel materials, the high surface-area-volume (S/V) ratio will significantly improve the sensitivity. The result of high S/V ratio is that a vast part of the atoms in the material are situated close the surface. Above mentioned feature stimulates the surface atoms to perform a more efficient role in determining the electrical, chemical, and physical properties of the nanomaterials. That is why nanomaterials are highly sensitive and useful in molecular sensing applications. The small size of these nanomaterials is another important feature that makes them ideal candidates for POCT devices. The other property of nanomaterials that makes them the ideal material to create connection between scientific instruments and biological molecules is their comparable size with biological samples, such as viruses, cells, nucleic acid, proteins, etc. As well as their very great smallness would allow compacting a large number of sensing segments into a small chip of an array device, which can be used in multiplexed sensing of a panel of disease markers. Although the advantages of the FET nanobiosensors are attractive, development of such devices into commericalizable POCT devices are still challenging. Several important issues need to be well explored and addressed before potentially commercializing the technology.

Device fabrication cost

One important factor for commercializing any technology is the cost-efficiency. Device fabrication can be quite costly if the materials are difficult to obtain and the processes are too complicated. In order to control the fabrication cost, the semiconductor materials used need to be abundant materials or materials easy to synthesize, e.g., Si materials, ZnO, In2O3, etc. During the fabrication process, the most conventional photolithography is optimal because of the low-cost of materials and simple process. However, photolithography can only define the dimensions at the micrometer scale. Therefore, a good design of the device structure is desired to relax the dimension requirement and still maintain the same nanoscale characteristics. Moreover, large-scale fabrication capability is also a key feature to further reduce the fabrication cost. And this can also be fulfilled by applying the CMOS-compatible photolithography process during the fabrication.

Consistency

A good product requires delivering consistent testing results under any circumstances. Large-scale fabricated transistors need to maintain very similar if not identical

electrical performances among different devices. The low device-to-device variation is one of the most important aspects to consider when designing the fabrication process of the transistors. Low device-to-device variation also ensures the high device yield. The almost 100% device yield saves time and labor for additional device screening process before actually packaging the final product. Reliable and efficient surface functionalization scheme for the semiconductor channel is another important feature to provide testing result consistency.

CONCLUSION

This type of technology is developing swiftly and according mentioned information, FET-based nanobiosensors have already proved as a device with highly potential applications including drug discovery and health monitoring. In this review, nanobiosensors is introduced and current research trends in field-effect transistor of nanobiosensors, surface functionalization of semiconductor materials and finally commercialized POCT devices are discussed. Also, I summarized several parameters influencing the sensing curves in real time detection experiments, such as sensitivity, selectivity, and settling time.

The sensitivity is mainly affected by nanomaterial dimensions, doping levels, device geometry, gating method (back gate or liquid gate) ionic strength of the buffer, size of the capture probe, and applied gate voltage effect.

The selectivity of these devices is directly related to the binding affinity of the capture probe for the analyte. The settling time, the time it takes to capture the analyte and produce a binding signal, is mainly affected by the type of delivery system which is used (microfluidic or mixing cell). So, according to mentioned investigations in this review, using nanomaterials is important feature that makes FET-based biosensors ideal candidates for POCT devices. It is clear that development of such devices into commericalizable POCT devices are still challenging. Several critical issues such as Device fabrication costs and Consistency need to be well explored and addressed before potentially commercializing the technology.

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