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REVIEW ARTICLE

A review on nanomaterial-based field effect transistor technology for biomarker detection

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Abstract

Field effect transistor (FET) based sensors have attractive features such as small size, ease of mass production, high versatility and comparably low costs. Over the last decade, many FET type biosensors based on various nanomaterials (e.g. silicon nanowires, graphene, and transition metal dichalcogenides) have been developed to detect various classes of biomolecular targets due to their integration into portable and rapid test systems, both for use in the clinical lab and in point-of-care testing. This review (with 197 refs.) starts with an introduction into the specific features of FET biosensor technology. This is followed by a description of the essentials of methods for immobilization of recognition elements. The next section discusses the progress that has been made in FET based biosensors using semiconducting nanostructures composed of silicon, graphene, metal oxides, and transition metal dichalcogenides. A further section is devoted to microfluidic systems combined with FET biosensors. We then emphasize the biosensing applications of these diagnostic devices for analysis of clinically relevant biomarkers, specifically to sensing of neurotransmitters, metabolites, nucleic acids, proteins, cancer and cardiac biomarkers. Two tables are presented which summarize advances in applications of 1D and 2D nanomaterial-based FETs for biomarker sensing. A concluding section summarizes the current status, addresses current challenges, and gives perspective trends for the field.

Keywords Biosensor · Semiconductor nanostructures · 1D materials · 2D materials · Silicon · Dichalcogenides · Analytical performance · Nucleic acid · Protein · Cancer

Introduction and features of FET biosensor technology

Current sensing methods are capable of accurate and specific detection of biomarkers, but they are considered unsatisfactory to meet the challenges of rapid, low-concentration and inexpensive measurement [1, 2]. These limitations can be overcome by developing new and reliable field-effect transistor (FET)-based biosensors, providing label-free, sensitive, fast, and low cost analyses [3, 4].

FET-based biosensors are a class of electrical biosensors which offer distinct advantages over some other systems owing to their mechanism of action. Accumulation of charged analyte species at their solution interface leads to a modulation of the resistance of a thin channel between source and drain electrodes. These devices have great potential to become one of the major sensing technologies for medical diagnostics particularly for point-of-care (POC) applications [5–7].

In the last few decades, great progress have been made in the design and fabrication of FETs using nanomaterials. Nanomaterial based FETs have received increasing attention as a powerful diagnostic platform due to their unique electronic properties, ultra-small dimensions and real time biological detection with high sensitivity and dynamic range [3, 5, 8]. The sensitivity of such nanoelectronic platforms is particularly great, spanning biomarker concentrations ranging from micromolar to zeptomolar and even in some cases permitting the measurement of single molecules or particles [9–11].

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Here, we highlight the properties of one- and two-dimensional semiconductor nanomaterials enhancing FET based biosensor performance and then focus on the biosensing application of nano-FETs for analysis of clinically relevant biomarkers. An important class of 1D materials, carbon nanotubes (CNTs), has been recently reviewed in this context and therefore will not be addressed here [12]. We next explain how these diagnostic devices can improve analyses in terms of linear range and limit of detection (LOD). Finally, an overview of the new frontiers and the challenges in this field will be presented.

Immobilization of recognition elements

One of the crucial steps in biosensor design is the development of reliable immobilization methodologies for stabilizing biomolecules onto material surfaces. Important considerations include maintaining the receptor's biophysical properties and binding characteristics, as well as reducing nonspecific binding/adsorption events. Several approaches are available and selecting the optimum one for a particular application depends on different factors such as the transduction principle, the nature of the biorecognition element and the nature of the analyte to be detected [2, 13, 14].

Biorecognition elements include bioreceptors such as antibodies and nanobodies [15–17], nucleic acids [18, 19], enzymes [20, 21], and even larger biological units, such as whole cells [22] and phage particles [23, 24]. Immobilization of recognition elements can be accomplished using different approaches, including adsorption, covalent bonding, crosslinking, entrapment, and encapsulation [18, 25–28]. Covalent bonding and crosslinking belong to the chemical methods of immobilization, while adsorption, entrapment, and encapsulation are placed under physical methods. In the physical method, the recognition element is directly adsorbed onto the surface and binding is achieved through a non-covalent interaction, such as hydrogen bonding, van der Waals force, electrostatic or hydrophobic interactions. Chemical methods result in stronger, covalent interaction between recognition element and the support material through their functional chemical groups [2, 13, 14]. Nevertheless, considering the inherently complex nature of the structure of biomolecules, it can be concluded that there is no one best approach for immobilizing all biorecognition elements.

Silicon nanowire-based FET biosensors

SiNWs are 1D nanostructures composed of a single crystalline silicon core which is coated with an amorphous silicon oxide sheath. SiNWs can be either n-type or p-type with a cross-sectional diameter of 2–100 nm and lengths in the micrometer range [29, 30].

The high sensitivity of SiNW- FET devices arises due to their small cross sectional area and large surface-to-volume ratio. Both the "top-down" and "bottom-up" methods have been used to fabricate the SiNW component of FETs. The "top-down" SiNW-FETs are constructed from a silicon-on-insulator (SOI) wafer by electron-beam lithographic processes combined with etching and doping techniques. Through these standard procedures, SiNW channels (light doping) and source/drain electrodes (heavy doping) can be defined to form SiNW-FET devices, in which the width of the SiNWs can reach the scale of ~100 nm [29]. Compared with the top-down approach for the *SiNW*-FET fabrication, the bottom–up approach is attractive as it results in the generation of high-quality, small diameter (3–5 nm) and single-crystalline nanowires (NWs). On the other hand, the process to prepare "bottom-up" SiNW-FETs generally starts with the growth of SiNWs in a chemical vapor deposition (CVD) reaction via the vapor-liquid-solid (VLS) mechanism, followed by nanowire assembly. Finally electrode fabrication is performed via photolithographic or electron beam lithographic procedures, completing the construction of functional devices [31–33]. A number of methods have been developed for controlled alignment and assembly of 1D SiNWs into desired structures. These methods include Langmuir-Blodgett (LB) [34], blown–bubble (BB) [35], flow based [36], electric field [37], and contact printing alignment [38]. The fundamental objective of these methods is to supply well-defined and controlled assembly of individual NWs on substrates that will then be applied for the development of functional devices multiplexed for the real time detection of biomarkers [39].

In a typical SiNW-FET system, the bio-recognition elements are immobilized on the surface of the SiNW channel to capture a specific target analyte. When the biorecognition receptors are exposed to the target molecule, the surface potential undergoes changes and the channel conductance is modulated. The conductance changes lead to current changes which provide the analytical signal which is further processed by an electronic detection system. Surface modification is an important issue for the fabrication of SiNW-FET biosensors. Silane coupling agents (organosilanes) are commonly used to enable the presentation of various functional groups such as thiols, epoxides, aldehydes, and primary amines on the silicon oxide surfaces. The most widely used silane coupling agents for the immobilization of analytes on SiNW surfaces are aminopropyltriethoxysilane (APTES), 3-mercaptopropyltrimethoxysilane (MPTMS), and 3-(trimethoxysilyl) propyl aldehyde, which introduce amino, thiol, and aldehyde functional groups, respectively, on the surface [40–44]. In addition to using the oxide layer on the SiNW surface, Heath's group [44] also reported the removal of the native oxide layer of SiNWs by submerging the NWs into dilute hydrofluoric acid (HF). HF-*etching* of the oxide layer of SiNWs produces hydrogen-terminated silicon surfaces, which

can react with alkenes and alkynes to form a Si-C linked monolayer. Cicero et al. [45] reported this method for the first time in 2000, however, it still remains attractive because of its high efficiency.

A number of basic parameters can be optimized to improve the sensitivity of SiNW-FETs including wire size, doping concentration and Debye screening length. For instance, SiNWs with smaller wire size and a small thickness of the silica layer, permit the analyte induced external electric field to affect the entire cross section of the nanowire. This is due to the drastic increase in the *surface*-to-*volume ratio* of thin wires. The doping concentration is also an important factor affecting the sensitivity of the SiNW-FET device [46]. It has been demonstrated that making use of SiNWs with lower doping ratio (10^{17} atom/cm^3) can increase the detection sensitivity of a device by 3-fold compared to a device with a heavy dopant (10^{19} atom/cm^3) concentration. This phenomenon is attributed to a diminution of the screening effect by electron carriers/holes in the SiNWs [46]. The other well-known factor that affects the sensitivity of the SiNW-FET is the Debye screening length. In SiNW-FETs, this length is the distance away from the semiconductor surface over which significant charge separation can occur. In fact, the Debye length is directly proportional to the distance over which the NWs can respond to a change in charge. In other words, a long Debye length is highly desired to insure that even a small change in local charge can be monitored by the NW. The Debye length can be enhanced by using a dilute buffer solution with a low concentration of electrolytes. However, this low ionic strength of the electrolytic buffer solution may influence the structure and/or biological activity of the target biomarker. The Debye length (λ_D) is calculated using the following formula: $\lambda_D = 0.304(I)^{-0.5}$, where I is the ionic strength of the buffer solution used for sensing. Therefore, to maximize signal collection, an electrolytic buffer solution with an appropriate Debye screening length should be employed [46–51].

SiNW-FET nanosensor devices have been designed for the detection of a wide variety of targets, including deoxyribonucleic acid (DNA), proteins, small molecules, metal ions and chemical species, single virus particles, and even cells [44, 50, 52–55].

Graphene-based FET biosensors

Graphene, one of the first 2D nanomaterials to undergo significant development, is a single atom-thick layer of sp^2-hybridized carbon atoms arranged into a honeycomb lattice by covalent bonds. This 2D nanomaterial, which can be considered to be the building block of many other carbon allotropes (CNTs, fullerenes, and 3D graphite), has attracted special attention due to its outstanding properties. These include good thermal (5000 W m^{-1} K^{-1}) and electrical conductivity (550 S cm^{-1}), high surface area (2630 m^2 g^{-1}), high optical transmittance (97.7%), excellent mechanical strength (Young's modulus of ~1 TPa) and high carrier density (10^{13} cm^{-2}). In addition, graphene possesses an exceptional carrier mobility, of up to 200,000 cm^2 V^{-1} s^{-1} at room temperature, which is almost 2 orders of magnitude higher than the conventional semiconductor, silicon [3, 56].

The mobility of charge carriers for graphene isolated from graphite, suspended graphene devices, and CVD grown graphene on a silicon dioxide (SiO_2) substrate have been reported to be more than 10^7 cm^2 V^{-1} s^{-1}, 10^5 cm^2 V^{-1} s^{-1}, and 4×10^3 cm^2 V^{-1} s^{-1}, respectively [8]. As compared to SiNWs and CNTs, graphene materials possess low intrinsic noise, higher carrier mobility, ambipolar field-effect characteristics as well as large specific detection area.

Moreover, in a single layer of graphene, all the carbon atoms are able to interact with the analyte, potentially leading to high sensitivity when compared to other "bulk" nanomaterials such as SiNWs [4].

Graphene can be produced by either bottom-up or top-down processes. The bottom-up approach relies on the growth of graphene onto different substrates, while the top-down method refers to mechanical exfoliation of graphite, which is a rapid way to obtain both single and few layer graphene [5]. Despite production of high-quality graphene sheets using the exfoliation processes, this method is not suitable for mass production of large area graphene based devices. Over the years, other synthesis technologies such as CVD on various metal substrates, epitaxial growth on single-crystalline silicon carbide (SiC) substrates, and reduction of isolated graphite oxide (GO) flakes via several methods (e.g. thermal, chemical and electrochemical) have been widely employed for graphene production [57, 58].

It is worth noting that the CVD method is currently the most efficient way to synthesize uniform, high quality, low cost, and large area graphene films. This allow researchers to develop multiplexed and high density graphene based devices on a single chip for many sensing applications including FET devices, chemical and biological sensors [59, 60].

A graphene-FET (G-FET) can be constructed by placing a graphene channel across two electrodes, the source and the drain contacts. These devices are generally fabricated using standard lithography and metal evaporation processes to pattern and deposit the metal electrodes [61]. In the G-FET devices, the graphene active layer acts as a zero band gap semiconductor, exhibiting ambipolar field-effect behavior (V-shape transfer curve) since the Fermi level can be shifted by the application of a bias voltage between graphene and the source electrode [61]. This field induced fermi level shift can switch the channel to either p-type or n-type.

Other properties recommending graphene for use as a channel material for the development of FET based biosensors include its excellent chemical stability and biocompatibility. There are three forms of graphene that have been applied to

construct graphene based FET biosensors, including CVD-grown graphene, reduced graphene oxide (rGO), and graphene flakes [59].

For biosensing applications, the graphene surface is modified by immobilizing bioreceptors (e.g. antibodies or single strand DNA probes) through direct adsorption or via a linker molecule which enables the bioreceptor to be oriented for specific binding to the target biomarkers. The linker molecule can be immobilized on the graphene surface through covalent or non-covalent binding [62].

Covalent functionalization of graphene generally occurs through reaction with the sp2 carbon atoms of the graphene lattice, which in turn induces defects and degradation of the local electronic properties. In contrast, non-covalent functionalization is a preferred functionalization method, because it provides a way of attaching new functional groups to graphene without affecting its structure and electronic properties [5, 63]. Electrochemical polymerization, π-π stacking, hydrogen bonding, and van der Waals forces are commonly used for noncovalent modification of graphene. For example, graphene can be noncovalently modified with the pyrene-derivative pyrenebutanoic acid succinimidyl ester (PBASE), through π-π stacking. This treatment can easily prepare the surface for immobilizing bioreceptors such as nucleic acid capture probes [64, 65].

In general, the sensitivity of a G-FET biosensor can be tuned, or optimized by changing the gate voltage. Since the channel current responds rapidly to variations in gate voltage, including analyte induced potentials, due to the high carrier mobility of graphene, G-FETs are an ideal and fast platform for monitoring biological binding events.

A variety of G-FET biosensor devices have been constructed, demonstrating sensitive detection of various analytes including DNA [64, 66], micro ribonucleic acid (miRNA) [67], proteins [68], pathogenic virus [69], glucose [70], and neurotransmitters [11, 71] which are described in more detail in the following sections.

Transition metal dichalcogenide-based FET biosensors

The remarkable progress of the graphene based nanomaterials has inspired the research community to develop other 2D layered materials including boron nitride (BN), carbon nitride (CN), transition metal oxides (TMOs), and transition metal dichalcogenides (TMDs) [72, 73].

In particular, TMDs have attracted considerable research interest due to their outstanding electronic properties. As its name implies, TMDs consist of transition metal elements sandwiched between two chalcogen atoms with the formula MX_2. Where M is a transition element such as molybdenum (Mo), tungsten (W) or niobium (Nb) and X is a chalcogen such as sulfur (S), selenium (Se), or tellurium (Te). In bulk layered TMDs, the intralayer atoms (M & X) are covalently linked with each other while the interlayer interaction is driven by weak van der Waals forces, which allow thin layers to be easily separated via exfoliation. These materials can be classified into semiconducting, metallic, or superconducting depending on the different combinations of M and X elements [72, 74].

A single layer of TMD, which is 6–7 Å in thickness, is made up of the three atomic planes (X-M-X) with in-plane covalent bonds while the interactions between this layer and the substrate and the analyte medium are mediated by van der Waals forces. The TMDs of current interest for sensing applications possess intrinsic bandgaps which are tunable from 1.1 to 2.2 eV via their chemical compositions and layer thickness. The band structures change (i.e., the indirect band gap turns into a direct band gap) as the thickness of TMDs is thinned from bulk into mono- or a few layers, resulting in thickness-dependent sensitivity [75, 76].

Synthetic methods for the preparation of 2D TMDs nanosheets are similar to the case of graphene as described above. These methods include CVD growth, mechanical cleavage, chemical /liquid exfoliation, and wet-chemical syntheses [4, 60].

The unique features of TMDs, including a direct band gap and atomic thickness along with their excellent mechanical, optical, and electrical properties make them ideal candidates for developing next-generation high performance FET biosensors. As described below, they appear to be amenable to high-throughput and label free detection of biomolecules at extremely low concentrations (fM/sub-fM level).

The incorporation of semiconducting TMDs, in particular MoS_2, into FET biosensors has increased in recent years due to its inherent bandgap and relative chemical stability [77–79].

The presence of a band gap enables high switching or on/off current ratios which is useful for constructing FET devices. For example, a single layer of MoS_2 has a direct band gap of 1.8 eV which leads to very low leakage currents. Moreover, MoS_2 exhibits exceptional electronic properties such as good carrier mobility (700 $cm^2\ V^{-1}\ s^{-1}$), remarkable current on/off ratios (10^8), and a tunable band gap, making it very favorable for FET biosensor applications [4, 74]. MoS_2 FET based biosensors have been successfully applied to detect various biomolecules including glucose [80], DNA [81], miRNA [82], and cancer biomarker [83, 84].

Metal oxide-based FET biosensors

The metal oxides of most relevance as FET biosensors are 1D and 2D nanostructures which consist of one or more transition metals and oxygen. During the past decade, they have been widely used for the development of FET type biosensor due to their specific structural and electrical characteristics. Because the intrinsic electrical properties of these materials fall within a range compatible with electronic readout, they can work without

impurity doping. Zinc oxide (ZnO), indium oxide (In_2O_3), hematite (Fe_2O_3), tin dioxide (SnO_2), copper oxide (Cu_2O), gallium oxide (Ga_2O_3), and cadmium oxide (CdO) are some of the more common examples of metal oxides which can be produced in the form of 1D structures [85]. Up to now, various methods have been developed to generate them in different configurations such as nanorods (NRs), NWs, nanotubes, and nanobelts. 2D metal oxides, including binary metal oxides, ternary metal oxides, and hybrid metal oxides, are of great interest in various applications due to their electronic properties and high density of active sites for functionalization [86, 87]. Generally, "top-down" and "bottom-up" approaches have been used to fabricate many 2D metal oxide nanomaterials such as vanadium pentoxide (V_2O_5), manganese dioxide (MnO_2), cobalt oxide (Co_3O_4), titanium dioxide (TiO_2) and others [88].

One-dimensional ZnO nanostructures are composed of two interconnecting sub lattices of Zn^{2+} ions, in which each anion is surrounded by a tetrahedron of O^{2-} ions and vice versa. As an oxide semiconductor, zinc oxide is one of the most promising metal oxides for use in electrochemical sensors due to its ability to react with oxygen [89]. Additionally, ZnO nanostructures have several advantages such as possessing good chemical stability, low toxicity, intrinsic hydrophilicity, and high electron mobility [90]. It has prominent properties such as piezoelectricity, a wide direct band gap (~3.37 eV), photo absorption in the UV, and a high exciton binding energy of 60 meV. There are different configurations of ZnO nanostructures including quantum dots, nanotetrapods, NWs (<100 nm), and NRs (>100 nm). Generally, ZnO NWs [91] and ZnO NRs [92] are the most exciting materials for FET type biosensor fabrication due to their controllable and reliable electrical properties as well as high isoelectronic point (IEP; 9.5).

Gas-phase and solution-based growth approaches such as CVD and hydrothermal decomposition are available to synthesize ZnO nanostructures [93]. Various strategies have also been applied to improve the performance of ZnO nanostructure based FET devices including surface functionalization, doping, irradiation-induced modification, surface passivation, annealing and plasma treatment [92, 94]. In particular, ZnO seeded surfaces can be easily modified with metals and metal oxides to enhance the electron transport, reproducibility, and surface area of the channel [92, 95].

Among the metal oxide nanostructures, a unique and particularly interesting material is In_2O_3. In recent years, In_2O_3, as a semiconductor, has been extensively used for development of FET type biosensors owing to its high mobility (~1490 cm z^2 V^{-1} s^{-1}), superior electrical conductivity, inexpensive synthesis, air stability and good metal-semiconductor contact formation. It is a wide band gap semiconductor, with a direct bandgap of ~3.6 eV and an indirect bandgap of ~2.5 eV [96]. Various forms of In_2O_3 such as nanoparticles, nanowires, nanotubes, and nanobelts have been synthesized in order to improve the performance of these devices [97, 98].

TiO_2, also called titania, can crystallize in three distinct structures: rutile, brookite and anatase. TiO_2 deposition can be performed by various methods including sputtering [99], CVD [100], spray pyrolysis [101], pulse laser deposition (PLD) [102], anodizing Ti metal [103], and the sol-gel technique [104]. Generally, rutile or anatase and sometimes the amorphous state structure of TiO_2 are produced by the methods mentioned above [105].

Microfluidics combined with FET biosensors

Because of their small size, simplicity and compatibility with traditional semiconductor microfabrication processes, FETs can be incorporated into microfluidic platforms to develop hand held, on-site, miniaturized medical diagnostic tests. Microfluidic platforms enhance FET functionality by enabling automated small-volume sampling, pre-separation, and multiplexed detection of analytes, eliminating the need for laboratory facilities and skilled operators. Using multiple sensing elements provides more quantitative, accurate and reliable test results. Microfluidic devices (MDs) are commonly fabricated from silicon, glass, and polymer materials. These materials can be organized into three broad categories: inorganic, polymeric, and paper. More recently, polymers have gained popularity, because of the low cost fabrication process (e.g., molding, embossing and printing). Polymer-based materials can be divided into elastomers and thermoplastics. Among the polymers, polydimethylsiloxane (PDMS) is the most popular material used for microfluidic platforms because of its flexibility, optical transparency, biocompatibility and low-auto fluorescence properties. Moreover, PDMS can be easily bonded to silicon, glass, or another piece of PDMS through treatment with an oxygen plasma. New materials such as paper and cotton fiber have recently been introduced as low-cost platforms for microfluidic-based POC diagnostics [15, 106]. The use of paper or cotton fiber, with hydrophobic and hydrophilic areas, patterned with wax printing or oxygen plasma, provides a convenient way to manipulate liquid transport in the device. Paper microfluidics is an emerging and substantially different technology from conventional microdevices made from either traditional polymer or inorganic materials [107–110]. Recently cellulose fiber based materials, such as filter paper and chromatography paper have been employed to support FET systems [111–113].

Applications of nanomaterial-based FET biosensors

Significant effort has been directed towards the incorporation of nanomaterials into the design of FET based biosensors since they provide unique opportunities for improving the analytical performances in terms of sensitivity and specificity over traditional diagnostic methods [3, 5].

There are several characteristics, particular to nanomaterials, which suggest that their integration into FET devices can provide advantages for the detection of biomolecules. First, nanomaterials exhibit remarkably large values of the surface-to-volume ratio, effectively amplifying the detection signal through higher loading of the biorecognition elements, leading to enhanced sensitivity. Secondly, because they are often single crystalline, they can also display increased thermal and electrical conductivity, chemical stability, and compatibility with solution, which make them highly competitive as components for the development of high-performance FET devices. A third reason is that the smallest dimension of the nanostructures can be comparable with that of the biomolecules of interest, facilitating the electrostatic interaction with biological species at the molecular level. Finally, the increased capability for miniaturization and compatibility with microfabrication procedures make these sensors ideally suitable for the development of low-cost POC medical diagnostics [4, 114]. Other valuable features of miniaturized devices include reduced cost and sample consumption, fast detection, ease of multiplexing, and high throughput, which are not achievable with many conventional sensors [62].

Recently, many types of nano-FET biosensors using silicon nanowires (SiNWs), carbon nanotubes (CNTs), graphene, metal oxide, and transition metal dichalcogenidebased (TMDs) as the semiconducting channel have been developed. A recent literature search in ISI Web of Science, from 2010 to July 2019, indicated considerable research interest in employing different types of 1 D and 2 D nanomaterials in FET channels for biosensing application. As depicted in Fig. 1, graphene plays a dominant role (52%) followed by SiNW (22%), zinc oxide (ZnO, 9%), CNT (8%), molybdenum disulfide (MoS_2, 8%), and indium oxide (In_2O_3, 1%), in decreasing order. The following sections present several of these reports, highlighting the great potential of nano-FETs for analysis of clinically relevant biomarkers.

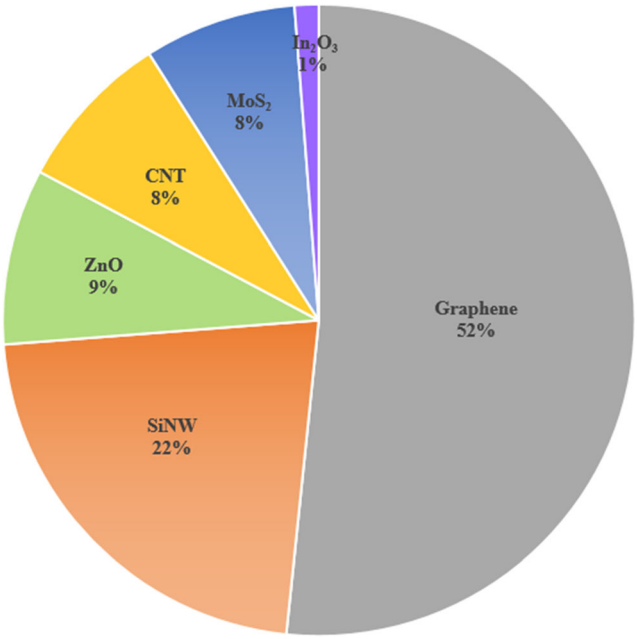

Fig. 1 Distribution of publications on one and two-dimensional (1D and 2D) nanomaterials in the FET based biosensor literature according to the ISI Web of Science from 2010 to July 2019

Determination of neurotransmitters

Neurotransmitters are endogenous chemical messengers which play a major role in transmission of signals across synapses from one nerve cell to another one to stimulate muscle or gland cells.

Various neurotransmitters including acetylcholine (Ach), dopamine (DA), epinephrine (EP), norepinephrine (NE), and nitric oxide (NO) serve as useful diagnostic biomarkers for neurological disorders (such as Parkinson's disease, Alzheimer's disease, and schizophrenia). They can also be used to monitor the progress and efficacy of treatments [115–117]. Considering the clinical importance of neurotransmitters, there is a push to develop assays with high analytical sensitivity for these markers. As compared to existing methods, FET-based biosensors offer advantages in cost, time, and simplicity, making them applicable to the clinic. These devices have been successfully applied to the detection of neurotransmitters including Ach, DA, and NO as discussed below.

In one example, a polymer modified G-FET type biosensor was adopted for Ach detection. The graphene surface was first functionalized with a copolymer containing carboxylic groups (to attach an enzyme) and pH sensitive groups (to detect the target analyte). The acetylcholinesterase was then covalently attached to the surface of the G-FET via amide bonds between the amino groups of the enzyme and carboxyl groups on the polymer. The subsequent hydrolysis of analyte Ach by multiple copies of the enzyme generated hydrogen ions on the graphene surface, which in turn yielded a change in sensor current due to the carrier doping effect. This biosensor was capable of determining Ach concentration with a LOD of 5 μM [118].

FET based biosensors have been modified to detect DA at the sub-nanomolar level [119, 120]. The poly- SiNW-FET was first developed by Lin et al. to detect DA at the fM level. In this approach, SiNW channels were first functionalized with APTES to introduce amino groups on the surface of the channels. These amino-functionalized SiNWs were then coupled to 4-carboxyphenylboronic acid (CPBA) using a cross-linking agent. Finally, the binding events, consisting of the reaction between DA and phenylboronic acid through DA–boronate ester bond formation, result in a negative change in charge, which can be recorded electronically [121]. Recently, another FET type biosensor based on SiNWs was developed to detect DA and neuropeptide Y (NPY) simultaneously by utilizing

their aptamers, immobilized on the SiNW surface, as recognition elements. The specific interaction of target analytes and aptamers resulted in the generation of a detectable signal. This multiplexed sensing platform was capable of detecting DA and NPY over the range from 10×10^{-9} M to 2.5×10^{-6} M and 100×10^{-12} M to 25×10^{-9} M, respectively [122].

In addition to SiNW, the semiconductor In_2O_3 has also been utilized for the sensitive detection of DA. In this work, sol-gel process and chemical lift-off lithography were used for In_2O_3 film production and electrode patterning, respectively. The ultrathin In_2O_3 film FET devices were then modified with aptamers, enabling the selective detection of target molecules with a linear detection range from 10^{-11} to 10^{-7} M [123].

G-FETs present an alternative approach to the detection of DA. Zhang et al. constructed a solution gated graphene FET by using a graphene/nafion-modified gate electrode. Incorporation of graphene/nafion composite films into the gate surface resulted in a negatively charged electrode interface, that would repel any negatively charged potentially interfering substances (such as ascorbic acid and uric acid), yielding improved selectivity and sensitivity (LOD < 1 nM) for DA [71].

FET devices enhanced with nanomaterials have also been applied to the task of fabricating high performance biosensors for NO. NO, a free gaseous signaling molecule, plays an important role in diverse physiological and pathophysiological pathway regulation [124]. NO has also been found to act in white blood cells, blood vessels and the central nervous system as a messenger molecule, endothelial-derived relaxant factor (EDRF) and neurotransmitter, respectively. Real-time and direct detection of NO is a challenge due to its short half-life, ease of oxidization, and low concentration. Xie et al. addressed this issue by assembling layer-by-layer rGO and iron-porphyrin functionalized graphene (FGPCs) onto the surface of a FET sensor. This combination combined the excellent electrical conductivity of rGO with the catalytic specificity of the metalloporphyrin, yielding a sensitive FET type biosensor for real-time monitoring of NO, and enabled detection over a broad linear range from 100 fM to 100 nM, with a LOD of 1.0 pM in phosphate buffered saline (PBS) and down to 10 pM in cell medium (Fig. 2) [11].

Determination of metabolites

Metabolites are the intermediate products of enzyme-catalyzed reactions that occur naturally within cells and are often small molecules [125]. Typical metabolites include glucose, uric acid, urea, cholesterol, lactate, hydrogen peroxide, creatine, creatinine, ketone bodies, xanthine and hypoxanthine. Quantitative measurements of metabolites as biomarkers are important in: i) making a diagnosis, evaluating its severity and effectiveness of treatment, ii) indexing of organ or tissue function and iii) determining risk biomarkers for predicting future development of diseases. The range of metabolite biomarkers detected by FET devices includes glucose, cholesterol, and urea, as explained in detail below.

Quantitative determination of blood glucose is routinely used to monitor diabetes. While conventional blood glucose analysis mainly relies on the enzymatic hydrolysis of glucose by glucose oxidase (GOx), some non-enzymatic approaches depend on the direct electro-oxidation of glucose using metal and metal oxide electrodes [126]. During the last few years, a variety of nanomaterials including metals (platinum, gold, copper), metal oxides (copper oxide, cobaltous oxide, nickel oxide, MnO_2), and carbon nanomaterials (CNT, graphene) have been used to explore their potential for application in non-enzymatic glucose sensors, making use of their electrocatalytic properties, chemical stability, and improved electron transfer properties [126, 127].

In FET biosensors, both the enzymatic and nonenzymatic methods have been employed for glucose detection. For instance, by using an amide linkage to covalently immobilize GOx onto an indium gallium zinc oxide (IGZO) channel, Du X et al. constructed a catalytic platform for highly sensitive and selective detection of glucose. In this assay, the oxidation of glucose by GOx yielded a significant decrease in pH, causing electron depletion in the n-type IGZO channel corresponding to the concentration of target analyte. The platform showed a wide linear range between 0 and 28 mM which covers the normal physiological range of glucose in interstitial and tear fluid (Fig. 3a) [9].

Hahn's group developed an enzymatic FET glucose sensor based on ZnO NRs. Using the seed-mediated growth approach, vertically aligned ZnO NRs were grown onto nozzle-jet printed silver electrodes on a flexible polyethylene terephthalate (PET) substrate. GOx was then adsorbed onto the surface of the ZnO NRs, followed by deposition of a nafion layer to avoid leaching of the enzyme and to block interferences. The FET device was able to determine glucose with a linear response ranging from 0.0 to 80 mM, a LOD of 0.07 mM, and a rapid response time of 10 s [128].

Recently, the same group extended this platform for non-enzymatic detection of glucose. Vertically-oriented ZnO NRs were produced using seeded growth then coated with nickel oxide nanoparticles. The results showed that NiO QDs significantly improved the electrocatalytic activity toward oxidation of glucose. This novel system generated two linear responses over a range between 1 nM - 10 mM and 10–50 mM at physiological conditions with a LOD of 0.026 mM [129].

Hahn's group also demonstrated that the ZnO NRs FET device can be employed for rapid and multiplexed detection of glucose, cholesterol, and urea in animal serum and blood. Here three different enzymes, GOx, cholesterol oxidase, and urease, were immobilized on the surface of three ZnO NRs FETs in an array by physical adsorption. Upon loading of target analytes onto the enzyme-modified FET devices, the

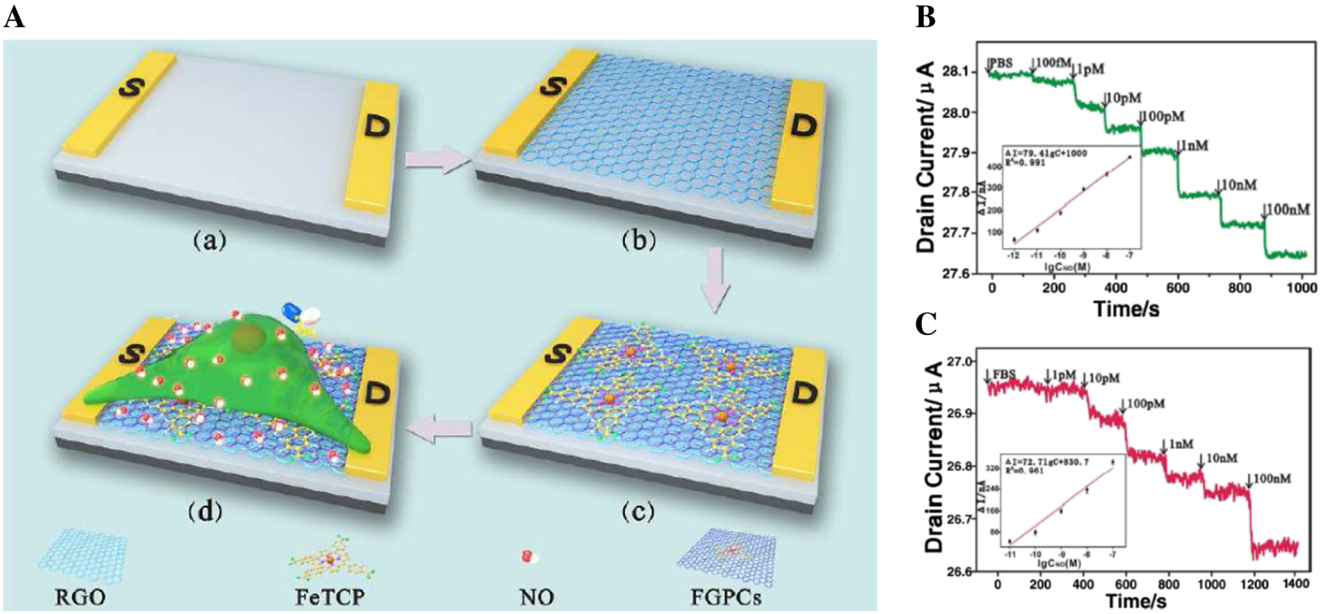

Fig. 2 **a** Schematic diagram of the rGO/FGPCs FET biosensor for real-time monitoring of NO release from cells. **b** Real-time electrical measurement at different concentrations of NO in PBS solution and (**c**) in the cell medium. Reprinted with permission from ref. [11]. Copyright 2016 American Chemical Society

enzymatic reactions induced localized changes in proton concentration, changing the conducting of the ZnO NRs and resulting in an increase in drain current. A LOD of 0.07, 0.04, and 0.032 μM was achieved for simultaneous detection of glucose, cholesterol and urea in a wide linear range (0.01 to 70 mM) [130].

Similar to ZnO NRs, In_2O_3 NRs have also been used for glucose evaluation. Using two shadow masks, In_2O_3 NRs and electrical contacts were patterned on PET substrates. The gold contacts were then modified with a mixture of GOx, which catalyzes the production of H_2O_2 during glucose oxidation, chitosan, and single wall CNTs. Finally, the attachment of positively charged ions (proton ions) to n-type In_2O_3 NRs acts as positive potential gating which increases the electron density in the In_2O_3 NRs and thus the current of the FET device. This noninvasive biosensor enabled the measurement of glucose over a wide linear range with a LOD of 10 nM [21].

Additionally, graphene and MoS_2 have been studied in FET glucose sensors. Zhang et al. developed a G-FET biosensor for glucose detection by immobilizing GOx on a platinum modified graphene gate electrode. This platinum modified electrode system exhibited excellent electrocatalytic activity for glucose oxidation and the redox current was increased by a fold compared to an unmodified electrode. The linear response range was 0.5 mM to 1 mM and the LOD was estimated to be 0.5 mM (Fig. 3b) [70].

Recently, Shan et al. reported a back gated MoS_2 FET sensor for glucose detection using a GOx enzyme modified channel device. In the presence of glucose, the H_2O_2 generated by the catalytic reaction caused an n-doping effect on the MoS_2 channel and thus an increase in the drain current was observed proportional to the glucose concentration (300 nM to 30 mM). This platform was capable of detecting 300 nM glucose with a short response time (<1 s) [80].

Determination of nucleic acids

Nucleic acids, including DNA and ribonucleic acid (RNA), function not only as carriers for transferring genetic information, but also as ideal clinical biomarkers for early diagnosis of relevant diseases and monitoring of the health status of patients.

Conventional techniques for nucleic acid testing often involve time consuming multiple steps including pretreatment, nucleic acid amplification, and target detection which make them inappropriate for practical applications in the clinic. Therefore, the development of fast, low-cost, and sensitive methods to detect very low concentrations of nucleic acid-based biomarkers in real samples is essential. To address this issue, many different types of biosensors (electrochemical, optical, and mass) have been developed for rapid and cost-effective measurements of DNA and RNA markers [18, 19, 131, 132]. Among these, FET based biosensor have been demonstrated to be highly efficient sensing platforms for the detection of nucleic acid biomarkers.

To date, many studies have focused on using G-FET biosensors for detection of DNA hybridization [66, 133]. For

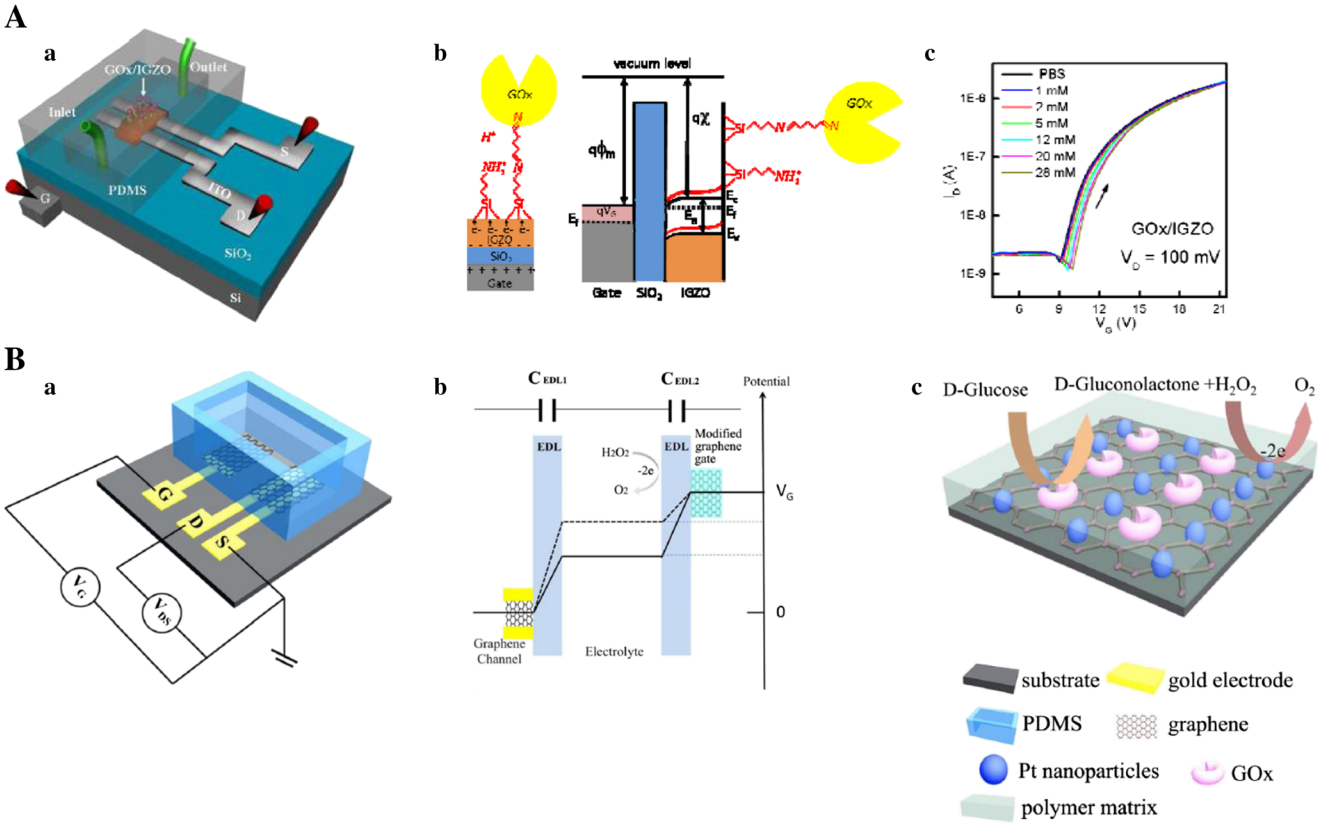

Fig. 3 **A** Schematic illustration of experimental apparatus for IGZO-FET sensor: (**A**-a) under electrochemical test and, (**A**-b) The role of positivity charged aminosilane group as an electron acceptor and the impact of positively charge aminosilane groups on band bending at IGZO surface. **A-c** Transfer characteristics for GOx functionalized IGZO FET after exposure to varying concentrations of glucose. Reprinted with permission from ref. [9]. Copyright 2016 American Chemical Society. **B**-a Schematic diagram of the glucose biosensor based on G-FET. **B**-b Potential drops across the two electric double layers (EDLs) on the surface of the graphene channel and gate. **B**-c The GOx-catalyzed oxidation of glucose and the reaction of H_2O_2 on the gate electrode. Reprinted with permission from ref. [70]

example, Loan et al. fabricated a G-FET device for sensitive detection of DNA based on the immobilization of probe DNA onto an ultraclean CVD grown graphene sheet. By employing residue-free gold-transferred graphene film instead of the polymethyl methacrylate (PMMA) mediated transfer process, 5 times higher sensitivity was achieved with a linear range from 1 pM to 100 nM and a detection limit of 1 pM. This finding demonstrates that surface cleanliness plays a key role in enhanced detection sensitivity and specificity [134].

Recently, another G-FET device for femtomolar detection of DNA using direct growth of graphene on sapphire substrates (without the need of metal catalyst and PMMA transfer) was developed. To implement detection, DNA probes were covalently immobilized onto a PBASE-modified G-FET surface by reaction of the amines of DNA and the succinimidyl ester group of PBASE. Upon hybridization with complementary target DNA, the conductivity of the G-FET changed in proportion to the concentration of the DNA target. The detection sensitivity of the assay (100 fM) was around 10 times lower than those achieved by transferred CVD graphene FET DNA biosensors (Fig. 4a) [135].

Like G-FET based biosensors, MoS_2 FET devices have also been employed for the highly sensitive detection of DNA hybridization. For example, Mei et al. designed an MoS_2 based FET biosensor for label-free ultrasensitive detection of DNA using phosphorodiamidate morpholino oligo (PMO) probes. The detection process involves the following steps: first, the prefabricated chip was treated with an APTES solution to generate positively charged groups on the FET channel. Second, the negatively charged MoS_2 suspension was deposited onto the APTES-coated device through electrostatic interactions. Third, the PMO probe was immobilized onto the PBASE-modified FET device to capture DNA targets. Finally, the PMO-DNA hybridization event was detected by analyzing the conductance change of the device before and after the hybridization step. Clear decreases in the drain-source current were observed upon addition of complementary target DNA with different concentrations (10 fM to 1 nM). The PMO-modified MoS_2 FET exhibited both enhanced detection sensitivity and specificity when compared to systems using DNA probes due to the neutral charge of PMO, which minimized the signal background and electrostatic repulsion of DNA hybridization [81]. In another study, a DNA

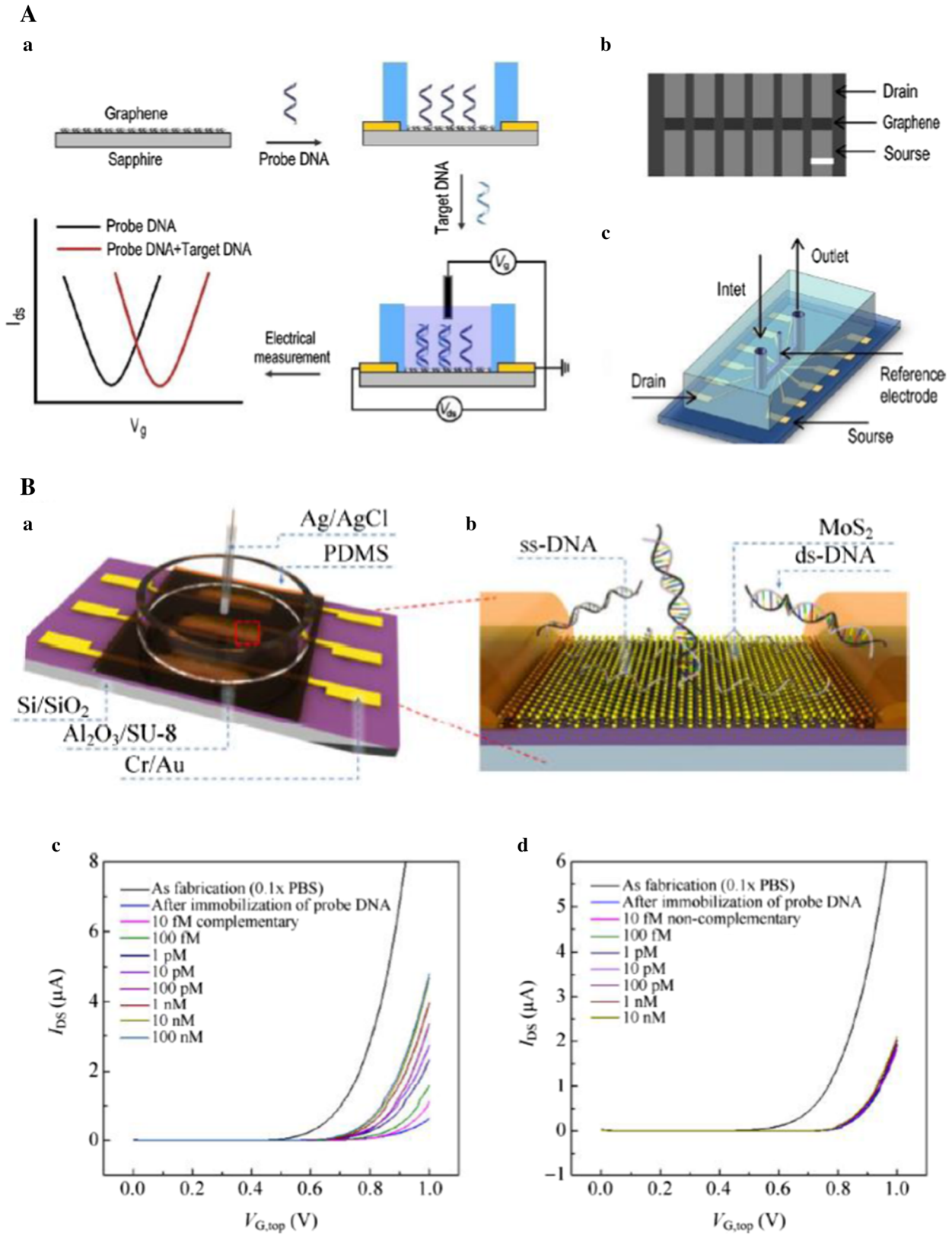

Fig. 4 **A**-a Schematic illustration of the solution gated G-FET biosensor prepared on a sapphire substrate, for detection of target DNA. **A**-b SEM image of the multi-G-FETs (scale bar, 100 μm). **A**-c Illustration of a G-FET array with a microfluidic channel on top. Reprinted with permission from ref. [135]. **B**-a Schematic illustration of combined back-gated and solution-gated FETs fabricated on an Si/SiO2 substrate and, (**B-b**) MoS_2 FET (**B**-c) Transfer characteristics of MoS_2 FETs with immobilized probe DNA molecules and hybridized with complementary and (**B**-d) non-complementary DNA. Reprinted with permission from ref. [136]

sensor based on a MoS_2 FET was fabricated with chemically synthesized few-layer MoS_2 with a sensing area of 300 × 6000 μm. The DNA capture probe was subsequently immobilized onto the sensor chip through direct adsorption without any linker molecule. When the hybridization process occurred, a shift of transfer curves toward the negative gate voltage (a left shift of the transfer curve) and increase in the drain current was observed. The assay detected analyte with sensitivity down to 10 fM with a wide dynamic range of 10^6 (Fig. 4b) [136].

There are also several studies which have demonstrated the use of FET devices for the rapid and sensitive detection of microRNAs (miRNAs), short noncoding RNA molecules with 18–25 nucleotides.

For examples, using a complementary metal oxide semiconductor (CMOS) compatible fabrication approach, researchers developed a SiNWs-based FET biosensor for the label-free and electrical detection of DNA/miRNA hybridization. In the first report, carboxyl-modified DNA capture probes were covalently immobilized onto the APTES-coated SiNW FET through amide bonds. Next, the hybridization events between target miRNAs and its complementary probe resulted in a measurable conductance change. The developed device was able to detect very low concentrations of target miRNAs (miR-21 and miR-205) in total RNA extracted from lung cancer cells and serum with a LOD of 1 zeptomole (i.e., 600 copies) Also, the platform was highly specific, allowing the detection of single-base mismatches [10]. Using a similar principle, He et al. developed another SiNWs FET sensor for specific detection of let-7b and snRNAU6 in standard solutions and cell extracted total RNA, respectively. A detection limit of 1 fM (for let-7b) and 0.2 μg/mL (for snRNAU6) with single-base mismatch discrimination was achieved using this platform [137].

rGO-FET biosensors decorated with gold nanoparticles (AuNPs) have also been employed for the highly sensitive detection of miRNA. In this sensor, cysteamine served as a modifier to facilitate the immobilization of peptide nucleic acid (PNA) probes onto the AuNP surface. Hybridization with complementary target miRNA produced a robust signal. This PNA-functionalized platform exhibited highly selective detection with a low detection limit of 10 fM. The phenomenon can be attributed to exceptional binding affinity and stability of PNA probes as well as to the signal amplification effects of the AuNPs [67].

In addition to G-FET devices, an organic electrochemical transistor (OECT)-based biosensor has also been modified with AuNPs binding sites to enable detection of miRNA. The device was fabricated using screen-printed carbon source and drain electrodes on a PET substrate and AuNPs –modified gold gate electrode. The thiolated DNA capture probe were subsequently immobilized on the AuNPs through the covalent Au-sulfur bond. When target RNA (microRNA21) was hybridized with the capture sequences on the AuNPs, source–drain current changes were observed proportional to the concentration of target RNA (5 pM to 20 nM). A detection limit of 2 pM was obtained, offering less sensitivity compared to SiNW and G-FET based biosensors [138].

Recently, Majd et al. developed a highly sensitive MoS_2 FET device for the detection of miRNA-155, a breast cancer diagnostic biomarker, using the direct adsorption of miRNA capture probes onto the MoS_2 surface and followed by hybridization with complementary target miRNA. A wide linear range (0.1 fM to 10 nM) along with a very low detection limit (0.03 fM) was achieved and these devices were demonstrated to be capable of detecting the target biomarker in spiked serum samples as well as in breast cancer cell line samples [82].

Determination of proteins

Proteins are one of the major biological macromolecules in living systems and play a main role in different physiological and pathological conditions.

The study of protein markers in body fluids may provide valuable information on human pathophysiology for the early diagnosis, monitoring, and treatment of disease [139, 140]. The present conventional techniques are effective in detecting or measurement of protein biomarkers, however, for the most part; they have major drawbacks such as the expense of instruments, and time consuming, complex protocols. Therefore, great efforts have been made toward the development of reliable biosensor tools to overcome these factors inhibiting adoption of important biomarker testing [141, 142]. Recent progress in the development of affordable analytical tools has relied on designs incorporating a combination of nanomaterials with "bulk" micro-materials. These combinations can significantly improve the performance of analytical devices for the ultrasensitive detection of various biomarkers while also increasing the functional and structural stability of these assay platforms [143, 144]. Thus, it is worthwhile to take a brief look at the FET-based devices, which are one of the most promising models of electrical biosensors, with potential applications for the onsite biomedical diagnosis via the detection of protein signatures of disease in the near future. This part of the review reports FET based biosensors for cancer and cardiac biomarker detection.

Cancer biomarkers

Cancer biomarkers are potentially one of the most valuable tools for the early diagnosis and staging of certain cancers, monitoring disease progression and assessing response to chemotherapy [17, 145]. Upon tumor formation, a change in the level of several biological markers can be detected in plasma or other body *fluids* [146]. Therefore, medical diagnostic assays must be selective, rapid, and sensitive enough to distinguish slight changes in the level of biomarkers in complex biological fluids. In the following sections, some examples

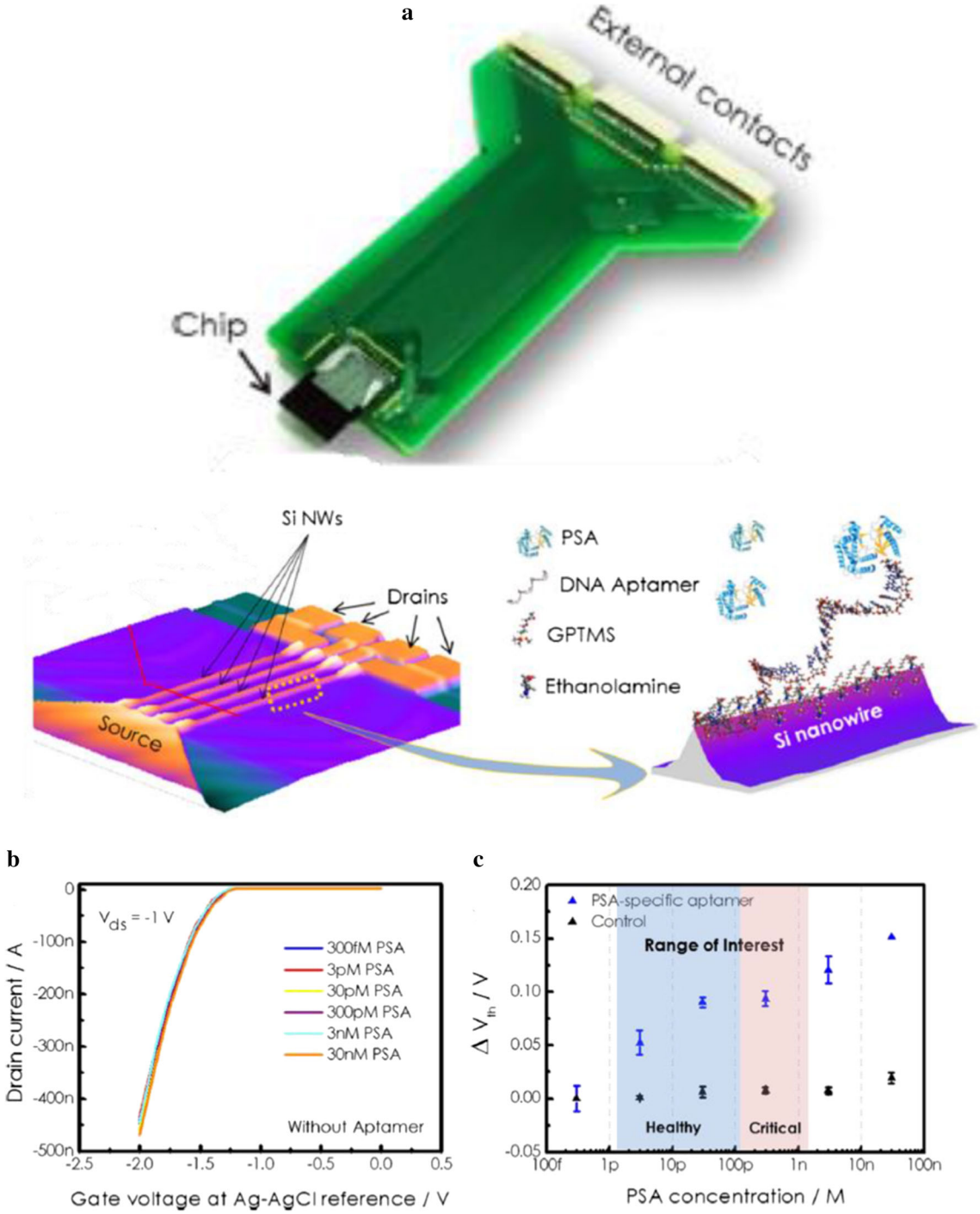

Fig. 5 **a** Photograph of: a top-down fabricated sensor chip with Si NW-ISFETs, the surface functionalization, and build-up of the biofunctional layer on the Si NW surface for label-free electrical detection of PSA. **b** Typical field-effect response of one Si NW-ISFET functionalized with the PSA-specific aptamer and tested with PSA concentrations varying from 0.3 pM to 30 nM. **c** The scatter chart summarizes the absolute Vth shifts as a function of increasing PSA concentrations for repeated experiments, where the results were baseline corrected to the smallest concentration of 0.3 pM ($n = 2$). Reprinted with permission from ref. [149]. (https://pubs.acs.org/doi/abs/10.1021/acsomega.8b00990). Copyright 2018 American Chemical Society (further permissions related to the material excerpted should be directed to the ACS)

of FET biosensors developed for detecting typically important cancer biomarkers are briefly described.

Prostate-specific antigen (PSA) PSA is a serine protease secreted by prostate *epithelial cell* into ejaculate and *blood and*

its level in serum is considered as an indicator of prostate cancer presence or recurrence in males [147, 148]. Rani et al. developed a p-type SiNW-FET array integrated with a microfluidic system for the label-free detection of PSA [149]. In this case, the SiNW channels were first covered with a layer of 3-glycidoxypropyltrimethoxysiloxane (GPTMS) to yield a hydroxyl-terminated surface which was subsequently attached to amine-modified aptamers via an amide linkage. The binding events between the target analyte and the aptamers caused significant shifts in threshold voltages that were proportional to the concentration of the analyte. This behavior can be attributed to an increase of positively charged molecules on the FET sensor surface. These sensitive devices exhibited a wide linear range from 3 pM to 30 nM with a LOD as low as 1.5 pM (i.e., 0.05 ng/mL) which covers the clinically relevant level of <4 ng/mL in healthy men (Fig. 5).

To further enhance sensitivity, effective surface modification was employed to improve the density and orientation of anti PSA antibodies on the SiNW-FET surface. After modifying SiNW channels with GPTMS-SH and 5 nm gold nanoparticles, antibodies were covalently immobilized on the sensor surface. This format allowed the determination of PSA down to 0.7 fM (23 fg/mL), 2 orders of magnitude lower than the conventional ELISA method [150].

Wang et al. used biofunctionalization of MoS_2 nanosheets to develop FET biosensors for real-time and ultrasensitive detection of PSA as a cancer marker. In order to immobilize anti-PSA antibodies on the MoS_2 channel, the fabricated chip was first covered with a dielectric layer of hafnium oxide (HfO_2), followed by treatment with APTES reagent. After that, the APTES-coated FET device was further modified with PSA specific antibodies to detect this target biomarker. Upon adding the biomarker, the immunoreaction of PSA with the antibody modified device led to an increase in the conductivity of the n-type transistor channel. The magnitude of the sensing response was proportional to the concentration of PSA, confirming the binding of the antibody to the PSA marker. This immunosensor exhibited high selectivity with a detection limit of 375 fM [83].

Based on a similar strategy, an alternative MoS_2-FET system was developed for ultrasensitive and reliable detection of the PSA biomarker in a dry environment. This dry-type MoS_2 device displayed high reproducibility and sensitivity with a detection limit down to 100 fg/mL [84]. Later, the same group improved the detection sensitivity of the biosensor using the hydrophobic character of MoS_2 which enabled the direct immobilization of antibodies onto the MoS_2 surface [151].

Carcinoembryonic antigen (CEA) CEA is a cell surface glycoprotein which has been employed for the clinical diagnosis of cancers. An increasing CEA level demonstrates the progression or recurrence of the disease. A label free antibody modified graphene FET type immunosensor was fabricated via surface modification for detection of CEA in PBS. Using a linker molecule which covalently binds to functional groups on the antibody while non-covalently binding to the graphene enables immobilization without significantly affecting the electronic properties of the graphene. 1-pyrenebutanoic acid succinimidylester (PYR-NHS) is a bifunctional compound that is composed of a pyrene and a reactive succinimide ester group. The aromatic pyrenyl group interacts strongly with the graphene using non-covalent π-stacking. The succinimidyl ester group reacts with the amine groups that exist on the surface of the antibody, resulting in the immobilization of anti-CEA antibody on the single layer graphene channel without disrupting its electronic structure. This G-FET biosensor obtained a LOD less than 100 pg/ml, and the dissociation constant (K_d) for the reaction between anti-CEA and CEA was evaluated to be 6.35×10^{-11} M [152].

In another study, SiNW-FET devices were integrated with PDMS microfluidic channels to enable the simultaneous determination of multiple analytes, including CEA. In this system, a dual-channel PDMS setup was employed to immobilize two antibodies on different SiNWs. This enabled the clinically reliable detection of the concentrations of two tumor makers simultaneously. A single-channel PDMS setup was also utilized to obtain the simultaneous detection of each tumor marker, including CEA and AFP, in serum. The linear dynamic range for CEA measurement was estimated to be from 50 fg/mL to 10 ng/mL [153].

Vascular endothelial growth factor (VEGF) *VEGF* is a signaling protein that plays diverse roles in vasculogenesis and angiogenesis. This important biomarker is associated with the progression of many cancers including breast, prostate, gastric, colorectal, lung, and cervical carcinoma [154–156]. Chen et al. fabricated a SiNW-FET biosensor by modifying the SiNW surface with antibody-labeled magnetic core/shell particles to detect VEGF in serum samples. When negatively charged target antigen (VEGF) binds to antibody-modified n-type NWs, electron carriers are depleted in the SiNW channel, causing a decrease in drain current. The generated signal was proportional to antigen concentration and displayed a linear response between 6.25 pg/mL and 500 ng/mL [157].

Human chorionic gonadotropin (hCG) hCG is a glycoprotein hormone secreted by the placenta in pregnancy to support ovarian corpus luteum. In addition to being a pregnancy biomarker, several studies have demonstrated the value of hCG as a key diagnostic biomarker in some cancers, including prostate, ovarian, and bladder cancer [158]. Recently, a label-free immunosensor was reported for hCG detection by Islam et al. [68]. In this work, hCG antibody was covalently immobilized

on the pyrene-modified G-FET to interact with target antigen. After antibody-antigen binding, an increase in the device resistance led to a right shift in the transfer curves. This assay exhibited a linearity ranging from 1 pg/mL to 100 ng/mL, with a LOD below 1 pg/mL.

Cytokines Cytokines, which include tumor necrosis factors (TNFs), chemokines, lymphokines, interleukins (IL) and interferons (IFNs), act as signaling proteins in a wide range of biological functions including immune regulation, inflammatory response, hematopoiesis, and cell proliferation. The association of changes in cytokine levels with defined types of cancers has been confirmed, thus their detection can provide useful diagnostic and prognostic information in cancer management [159, 160]. Approaches for single (IL6) and simultaneous detection of two cytokine biomarkers (IL8 and TNF-α) utilizing FET type biosensors are described next.

In the first report, a G-FETs immunosensor was successfully applied for the label-free detection of the protein IL6. In this work, GO was electrostatically deposited onto Si/SiO_2 covered with a layer of APTES and then reduced to decrease electrical resistivity. After the chip fabrication, anti-IL6 antibody was covalently immobilized onto the PBASE-modified G-FET, which was in turn followed by the affinity reaction with the target antigen, which resulted in a decrease of the drain current. This approach enabled the detection of IL6 down to the body normal value with a LOD of 1.53 pg ml [161]. In the second work, Zhang et al. demonstrated four-SiNW-FET arrays for multiplexed detection of IL8 and TNF-α in saliva [162]. In this immunoassay, corresponding antibodies were covalently attached on the APTES-modified SiNW surfaces and then the antibody- antigen binding was followed by monitoring the device resistance changes. According to the opposite charge of IL8 and TNF-α at the pH used for detection, an accumulation or depletion was observed on the surfaces of the SiNWs. This system permitted the detection of both biomarkers with LOD of 10 fg/mL and 100 fg/mL in PBS buffer and in artificial saliva, respectively.

Since the valuable levels of these three biomarkers are in the range of picomolar [159, 163], these FET biosensors demonstrated acceptable sensitivity and selectivity, making this a promising approach for development into devices for clinical applications.

Alpha-fetoprotein (AFP) AFP is a glycoprotein expressed by the embryonic yolk sac and the liver in the developing fetus. In the first weeks after birth, the secretion of AFP declines significantly. While normal serum levels of AFP in healthy adults is defined as less than or equal to 25 ng/mL [164], its concentration is highly increased in chronic liver disease, hepatocellular carcinoma (HCC), embryonic carcinomas, gastric

Table 1 1D nanomaterial FET biosensors for various biomarkers and their detection performances

Channel material	Analyte	Recognition element	Linear Range	LOD	Substrate of FET	Ref.
Single-crystalline boron-doped SiNW	DA	Aptamer	10^{-8} - 10^{-11} M	10^{-11} M	Si/SiO_2	[120]
N-type doped polycrystalline SiNWs	DNA	DNA probe	1fM-10 nM	1fM	Si/SiO_2	[172]
SiNW	DNA	DNA probe	1 fM-1 nM	1 fM	SOI wafer	[173]
Phosphorus-doped SiNW	DNA	DNA probe	0.1fM-10 nM	0.1 fM	Si/SiO_2	[174]
Polycrystalline SiNW	PSA	Antibody	5 fg/mL-500 pg/mL	5 fg/mL	Si/SiO_2	[110]
Boron-doped SiNW	VEGF	Antibody	1–7 fM	1 fM	SOI wafer	[175]
Polycrystalline SiNWs	IL8 and TNF-α	Antibody	–	10 fM	SOI wafer	[176]
SiNW	AFP	Antibody	100–500 ng/mL	100 ng/mL	SOI wafer	[177]
Boron-doped SiNW	α-fucosidase	Enzyme inhibitor (Fuconojirimycin)	1.3–250 pM	1.3 pM	Si/SiO_2	[178]
Polycrystalline SiNW	Apolipoprotein A II (APOA2)	Antibody	9.5 pg/mL-1.95 μg/mL	6.7 pg/mL	Si/SiO_2	[179]
Single-crystalline multi-channel SiNW	cTnI	Antibody	320 fM-3.2 nM	320 fM	SOI wafer	[180]
SiNW	cTnI	Antibody	0.092–46 ng/mL	0.092 ng/mL	SOI wafer	[181]
In_2O_3	Creatine kinase MB (CK-MB), cTnI, BNP	Antibody	0.1–3 ng/mL (CK-MB), 1–300 pg/mL (cTnI), and 10–90 pg/mL (BNP)	0.1 ng/mL (CK-MB),1 pg/mL (cTnI), and 10 pg/mL (BNP)	Si/SiO_2	[182]

Table 2 2D nanomaterial FET biosensors for various biomarkers and their detection performances

Channel material	Analyte	Recognition element	Linear range	LOD	Substrate of FET	Ref.
Palladium-decorated reduced graphene oxide (Pd-rGO)	NO	–	2–420 ppb	2 ppb	Si/SiO_2	[183]
Graphene	ACh	acetylcholinesterase	0.5–1000 μM	0.5 μM	sapphire	[118]
Graphene	22-mer DNA	DNA probe	100 pM-100 nM	100 pM	Si/SiO_2	[184]
Graphene	20-mer DNA	DNA probe	0.25–10 nM	10 pM	Si/SiO_2	[65]
Graphene	22-mer DNA	PNA probe	1 fM-100 pM	10 fM	Si/SiO_2	[185]
Graphene	21-mer DNA	Hairpin probe DNA	–	5 fM	Si/SiO_2	[186]
Graphene	DNA	DNA probe	–	single-nucleotide	Si/SiO_2	[64]
Graphene	RNA	DNA probe	0.1 fM-1 pM	0.1 fM	Glass	[187]
Graphene	PSA	Antibody	100 fg/mL-100 ng/mL	100 fg/mL	Glass	[188]
Graphene	hCG	Antibody	1 pg/mL-1 ng/mL	1 pg/mL	Si/SiO_2	[189]
Graphene	CEA	Antibody	10 pg/mL-45 ng/mL	337.58 fg/mL	Si/SiO_2	[190]
Graphene	IL 6	Aptamer	50–800 pM	12 pM	Si/SiO_2	[191]
Graphene	AFP	Antibody	0.1–250 ng/mL	0.1 ng/mL	PET	[192]
Graphene	proBNP	Antibody	100 fM-10 nM	10 pg/ml	Si/SiO_2	[193]
MoS_2	PSA	Antibody	10^{-5}-75 ng/mL	10^{-5} ng/mL	Si/SiO2	[194]
MoS_2	IL-1β	Antibody	1–500 fM	1 fM	Si/SiO2	[195]
MoS_2	TNF-α	Antibody	60 fM-6 pM	60 fM	Si/SiO2	[196]
TiO_2	cTnI	Antibody	1 ng/mL-10 μg/mL	0.238 ng/mL	SOI wafer	[197]

tumors and lung cancer [165, 166]. There are two reports based on SiNW-FET and G-FET immunosensors for the label-free and sensitive detection of AFP. In both studies, AFP antibodies were covalently immobilized on the modified sensing surface to bind the target antigen. Electrical measurements proved that both of these systems can quantify AFP with a concentration of 0.1 ng/mL in PBS, while the G-FET report also indicated the ability of the device to detect AFP concentrations as low as 12.6 ng/mL in plasma [164].

Cardiac biomarkers

Cardiac biomarkers are protein components of cell structures released into the circulation when the heart is damaged or stressed. They play an essential role in diagnosis and differential diagnosis of acute chest pain.

Troponin I Cardiac troponin I (cTnI), is a member of a complex of three regulatory proteins, namely troponin. This protein exists at low concentrations within the cytoplasm. It is released into the serum upon the death of cells and within 3–4 h of the onset of myocardial infarction (MI) symptoms. It can be used as a standard biomarker in patients presenting to the emergency department without chest pain. The level of cTn I in healthy humans is around 1 pg/ml, however it can rise to the level of 100 ng/ml in MI patients. FET type biosensors are portable, rapid, and inexpensive and offer a straightforward way to detect this cardiac biomarker. A honey comb like structured nanowire strategy was used to construct an FET type biosensor for detecting cTnI in buffer. A top down approach was applied to lithographically pattern the device, which was composed of lightly doped nanowires in a honeycomb structure and had an embedded Ag/AgCl pseudo-reference electrode. This patterning approach was employed in order to improve the electrical performance and increase the sensing area of the FET-device. Monoclonal antibodies against cTnI were covalently immobilized on the surface of the nanowire structure which had been prepared by functionalization first with APTES and then with glutaraldehyde (GA). The device exhibited n- type behavior with a relatively high ON-OFF current ratio, excellent specificity, and a detection limit around 5 pg/mL in buffer solutions with low ion concentration. The detection limit yielded by this method was the lowest reported in the literature compared to previous studies. Further, the LOD was nearly 8 times smaller than the existing diagnostic cut off for acute MI [167].

In the studies conducted by Arshad et al. [168], back-gate biasing was used to enhance the electrical conductivity of a fabricated FET-type biosensor. The sol-gel technique was used for deposition of a TiO_2 film to be used as the transducer in the channel area between the source and the drain. Two types of linkers (APTES and GA) were deployed to functionalize the surface of the TiO_2 thin film for covalent immobilization of cTnI antibody. The electrical characterization (I_d–V_d) of these devices confirmed the potential of this approach for the detection of cTnI, displaying a linear detection range from 10 μg/ml down to 1 fg/ml. This method offered the possibility of quantitative measurement of the cTnI with the sensitivity of 459.2 nA $(g/ml)^{-1}$ and demonstrated a detection limit of 1 fg/ml.

In a study by Fathil et al. [169], a substrate-gate coupling based FET biosensor device for the detection of cTnI biomarker was investigated. An n-type zinc oxide nanoparticle (ZnO-NPs) thin film was deposited through a sol-gel technique and spin coated onto the channel between two p-type top silicon layers, creating a p-n-p junction between source, channel, and drain, respectively. To produce a surface with aldehyde functionality for covalent attachment of the cTnI antibody, the surface of the thin film was treated with APTES, followed by GA, as a bi-functional linker. This new p-n-p device strategy demonstrated remarkable changes in drain current (I_d) and threshold voltage (V_T), between before and after cTnI target interaction with antibody, increasing the sensitivity of the assay, and providing a LOD down to 3.24 pg/ml.

Brain natriuretic peptide (BNP) BNP is a cardiac hormone which is produced principally in the heart ventricles. Studies have revealed that it can elevate in early heart failure (HF) [170]. Lei et al. presented a FET type biosensor capable of detecting the BNP biomarker in whole blood with high sensitivity and specificity [171]. The detection system was obtained by integrating a custom-made microfilter with platinum nanoparticle (PtNPs) decorated rGO. The biosensor was fabricated using drop-casting of rGO onto the pre-constructed FET chip and assembling PtNPs onto the surface of the rGO channel. Anti-BNP was covalently immobilized on the PtNPs surfaces, which was treated before with a thioglycolic acid in order to produce carboxylic groups on the PtNPs surface through Pt-S bond formation. In addition to antibody immobilization, the PtNP decoration increased the conductivity of the developed system and enabled the researchers to obtain a detection limit as low as 100fM.

Summary

Tables 1 and 2 summarize the sensing performance of 1D and 2D nanomaterial-based FETs for analysis of clinically relevant biomarkers. As is evident from the tables, major advantages of nano-FET biosensors are their high sensitivity and low detection limits. These devices can detect nM to fM level nucleic acids, proteins, and small molecules. For instance, cTnI, a cardiovascular biomarker, detected by nano-FET devices based on 1D nanomaterials (SiNW & In_2O_3) and 2D nanomaterials (TiO_2). The lowest detection limit of cTnI was achieved by a multi-channel SiNW- FET device (320 fM). The cancer biomarker PSA has been detected though SiNW, MoS_2, and graphene FET devices with detection limits of 5, 10, and 100 fg/mL respectively. Similar to the cTnI biomarker, the lowest detection limit for PSA was achieved by a SiNW- FET device (5 fg/mL). In addition to the low detection limit, the response time is relatively fast (seconds to minutes), allowing rapid detection and real-time monitoring of target analyte.

Much research has focused on finding a suitable channel material. Among various nanostructures, semiconducting SiNW based FETs exhibit high sensitivity and multiplex capability in detecting specific target molecules. The high sensitivity of the SiNW- FET devices arises due to their small cross sections and large surface-to-volume ratio. Despite obtaining high sensitivity by Si-NW-FET, practical challenges associated with their reliability and reproducibility (batch-to-batch variations) still need to be addressed. While the "top-down" fabrication strategy for production of SiNWs suffer from high manufacturing cost and low volume production, the bottom-up method, faces integrity problems due to limitations in deposition of small size active device components. These drawbacks in turn restrict the practical suitability of such structures.

Compared with 1D, the 2D materials have attracted more attention due to of their planar nature, providing good patternability and integrability. Therefore, 2D layered materials are promising candidates for the creation of FET-based devices. Among several 2D materials, graphene plays a dominant role (52%) in FET channels for biosensing application as mentioned earlier.

There are several factors including nanomaterial dimensions, doping concentration, device geometry, gate electrode (back gate/solution gate), the applied gate voltage, and the capture probe size all of which can affect the sensitivity of these FET biosensors. For instance, SiNWs with a smaller wire size and a small thickness of silica layer, permit the external electric field to go through the whole cross section of the nanowires. The doping concentration is also an important factor affecting on the sensitivity of the FET device. Additionally, the sensitivity can be improved by incorporating metal nanoparticles such as Au and Pt on the channel FET surface. For example, the decoration of an rGO-FET with AuNPs/PtNPs contributes to enhanced sensitivity and a femtomolar detection limit.

The selectivity of a biosensor is directly related to the specific binding of the capture probe (e.g., nucleic acids, antibodies, and enzyme) to the target analyte. In many cases improving the immobilization method increases the response to the immobilized recognition elements, raising the magnitude of the transduced signal and resulting in platforms with lower LOD and high selectivity. With the inclusion of multiplexed detection, FET devices will clearly be used to address challenges in early diagnosis and enhanced monitoring of the treatment of serious diseases, including cardiovascular diseases and cancer.

Conclusion and perspectives

We have highlighted practical information for researchers seeking an overview of recent progress to enhance their efforts to

develop FET type biosensors as POC devices for clinical applications. Thus, the most important advances of FET systems were discussed in conjunction with targeted classes of analytes and their potential for use in future clinical diagnostics. Although the development of rapid, low cost, sensitive and fully automated FET type biosensors for biomarker detection is imperative, there are still several major challenges that must be overcome before they become approved as POC tests.

There are three fundamental challenges in FET-based biosensor development. First, stable, reproducible immobilization of biorecognition elements onto the FET channel requires surface functionalization. Second, it is essential that the signal transduction mechanism employed, essentially the FET, must be manufacturable in large quantities with high reproducibility of intrinsic characteristic properties, including speed, reliability, shelf-life and amplification/gain. Third, high selectivity and low cross reactivity are required to create a FET type biosensor with true potential to become a POC device. Nevertheless, studies such as the ones reviewed here provide reason for great optimism that FET type biosensors will soon graduate from the laboratory and into the marketplace, especially for applications in early-stage detection of disease biomarkers. Currently, there are intense efforts, worldwide, directed toward incorporating nanomaterials such as SiNWs, graphene, TMDs and metal oxides, as sensing channels, into FET-based devices due to their high specific surface area, chemical stability, biocompatibility and environmental friendliness. However, due to the wide variation in results from one lab to another, it is difficult to compare the intrinsic performance of the components, including channel material type, in order to determine which is most suitable for further development. Furthermore, it is clear that the integration of microfluidic platforms with biosensing devices will be necessary to maximally benefit from miniaturization, automation of the analysis process and thereby fabricating multiplexed integrated analytical systems.

Therefore, future work in FET type biosensor development can be expected to proceed in the following order: (i) utilizing novel nanostructures as the semiconductor channel, to develop the most intrinsically sensitive device, (ii) covalently immobilizing recognition elements on this channel type, (iii) fully automating FET device use, in preparation for, (iv) fully integrating these sensors into deployable microfluidic systems.

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