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Interface-Engineered Field-Effect Transistor Electronic Devices for Biosensing

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Promising advances in molecular medicine have promoted the urgent requirement for reliable and sensitive diagnostic tools. Electronic biosensing devices based on field-effect transistors (FETs) exhibit a wide range of benefits, including rapid and label-free detection, high sensitivity, easy operation, and capability of integration, possessing significant potential for application in disease screening and health monitoring. In this perspective, the tremendous efforts and achievements in the development of high-performance FET biosensors in the past decade are summarized, with emphasis on the interface engineering of FET-based electrical platforms for biomolecule identification. First, an overview of engineering strategies for interface modulation and recognition element design is discussed in detail. For a further step, the applications of FET-based electrical devices for in vitro detection and real-time monitoring in biological systems are comprehensively reviewed. Finally, the key opportunities and challenges of FET-based electronic devices in biosensing are discussed. It is anticipated that a comprehensive understanding of interface engineering strategies in FET biosensors will inspire additional techniques for developing highly sensitive, specific, and stable FET biosensors as well as emerging designs for next-generation biosensing electronics.

1. Introduction

Highly sensitive and precise detection of chemical and biological molecules is essential for disease diagnosis, health monitoring, and pandemic screening.[1–5] Up to now, a variety of analytical techniques have been developed to achieve efficient biomolecule identification.[6–11] Among these assays, electronic devices based on FETs have attracted increasing attention. A typical FET biosensor is a three-terminal device composed of drain, source, and gate electrodes, a semiconductor channel, as well as biorecognition elements.[12] The current between the drain and source electrodes could be readily modulated by the gate electrical field, enabling the signal amplification capability of FET biosensors.[13,14] In particular, FET-based electronics exhibit superb performance in the identification of trace biomolecules at picomolar (pM) or even attomolar (aM) levels.[15,16] Additionally, FET-based electronic devices demonstrate remarkable capability in rapid and label-free detection of the analyte, as well as ease of integration.[17,18] Till now, FET-based electronic devices have been widely employed in chemical sensing, biomarker detection, drug and pathogen screening, and continuous health monitoring, promising their great potential in point-of-care testing (POCT) and remote healthcare.[19–22]

When FETs are used as chemical or biological sensors, analytes could change one or several parameters of the semiconductor channel under the electric field, which in turn generates variations in the current or potential signal.[17,23,24] Specifically, in the presence of targets, the biorecognition elements will concentrate the targets at the solution/solid interface, and then alter the charge density of the semiconductor channel. Subsequently, the gate electric field, usually perpendicular to the channel, will change the carrier mobility, doping level, or capacitance of the semiconductor material, and generate variations in the output signal.[25] Clearly, the solution/solid interface, including the channel material and the recognition elements, is the core of FET biosensors, where the specific recognition of analytes and signal transduction are completed.[3,26,27] Till now, in order to achieve highly sensitive, selective, and stable biosensing, there have been an increasing number of investigations working on the optimization of the semiconductor channel and biorecognition elements.[28–31] These attempts involve the modulation of channel materials, including surface morphology and interfacial engineering,[32–34] as well as the regulation of biorecognition elements through the structural design of antibodies and nucleic acid probes.[35–38] In consideration of the rapid development of interface-engineered FET-based electronic devices, a systematic overview of the interface engineering in FET biosensors would contribute to the understanding of the design principles of high-performance

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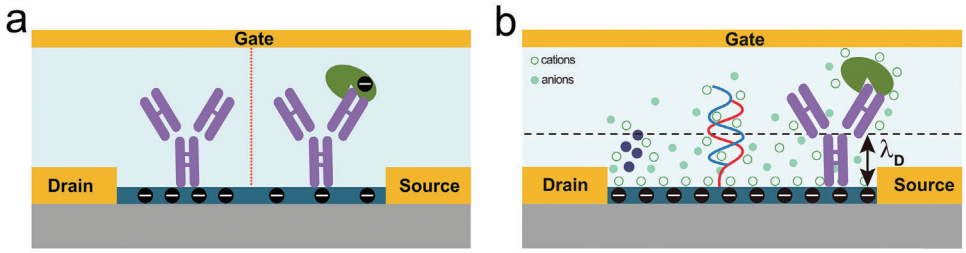

Figure 1. a) The mechanisms of FET-based electronic devices in biosensing. b) Schematic of the Debye screening effect and Debye length in FET biosensors.

electronic devices based on FET sensors, and may further promote the applications of the electronic devices in practical scenarios.

In this perspective, we summarized the engineering approaches in developing high-performance FET biosensors through sensing interface regulation. The strategies regarding nanostructured channel materials and biorecognition molecular design were comprehensively summarized. Next, the applications of interface-engineered FET biosensors in biosensing, including the identification of disease biomarkers, such as proteins, nucleic acids, small molecules, and pathogenic microorganisms, as well as dynamic monitoring of cell secretion processes under stimulation were comprehensively reviewed. For a further step, the design of point-of-care electronic devices based on interface-engineered FET biosensors to achieve on-site testing and real-time monitoring was summarized. Notably, the challenges and opportunities of interface-engineered electronic devices faced were discussed. It's expected that this work will contribute to the design of highly sensitive, selective biosensing interfaces, and high-performance electronic devices, as well as offer guidelines for their applications in clinical samples testing and persistent monitoring under physiological conditions.

2. Interface Engineering of FET Biosensors

As above mentioned, the electrostatic interaction between biomolecules and solution/solid interfaces plays a crucial part in FET biosensing (**Figure 1**a).[17,24,39,40] However, due to the high ionic strength of the biological media, the biomolecules would be surrounded by counterions, and an electrical double layer (EDL) would be formed on the channel surface. As a result, the effective charge of the target and the sensing interface will be severely screened, which will weaken the electrostatic interaction between them.[41–43] The charge screening effect, widely known as the Debye screening effect, would compromise the detection capability of FET biosensors (Figure 1b).[17,43,44] Based on Debye–Hückel equations, the thickness of the counterion shielding layer formed on the surface of the charged nanochannel, also known as Debye length (λ_D), could be calculated as follows:

$$\lambda_D = \sqrt{\frac{\varepsilon k_B T}{2 N_{Ae}^2 I}} \quad (1)$$

where ϵ is the dielectric constant of the electrolyte; k_B, T, and N_A represent Boltzmann's constant, Kelvin temperature, and Avogadro number, respectively; I is the ionic strength of the electrolyte, and e is the elementary charge. To some extent, the value of λ_D reflects the effective distance of electrostatic interaction between charged molecules and the biosensing interfaces.[25]

To overcome the Debye screening effect in FET biosensors, a low-concentration electrolyte solution is often employed for testing. For example, the Debye length could be enlarged from 0.3 to 7.0 nm following the decrease of ion concentrations of phosphate buffer saline (PBS) from 10 to 0.1 mM.[45,46] However, it is gradually noted that the biomolecular conformations are often disrupted under a low ionic strength solution, resulting in a decreased binding affinity between targets and biorecognition elements.[47–49] Hence, some strategies have been proposed for the regulation of the Debye screening effect through engineering the nanostructure of channel materials and biorecognition elements. They can be simply divided into two categories, including enlarging the Debye length and narrowing the distance between targets and the semiconductor channel (**Figure 2**, **Table 1**). Approaches to modulating the structure of sensing materials and biorecognition layers in FET-based biosensing devices for escaping from the Debye screening effect are elaborated in more detail in the following sections.

2.1. Interface Engineering of Channel Material

According to the Debye–Hückel equation, ion distributions on the sensing materials directly determine the Debye length of FET biosensors.[34] Currently, most FET biosensors are fabricated with a flat sensing interface, and the dense EDL formed on the flat interface would result in a relatively severe Debye screening effect.[25] Decreasing the concentration of applied electrolyte solutions is not suitable for long-time monitoring in physiological environments.[60] In some previously reported works, the ion distributions and Debye length above the sensing interfaces could be regulated with programmed nanostructures of channel materials.[33] For instance, in a nanostructured interface with concave and convex regions, ions in the electrolyte solution tend to be enriched in the convex regions due to the charge accumulation effect.[61] Consequently, the ion concentration in the concave regions would be decreased and the Debye screening effect would be weakened. Another representative case is the surface modification of the channel material. The inclusion of a polymer layer or lipid layer could effectively shorten the distance between target molecules and the sensing interface, thus resulting in prominently improved detection performance.[51] In the

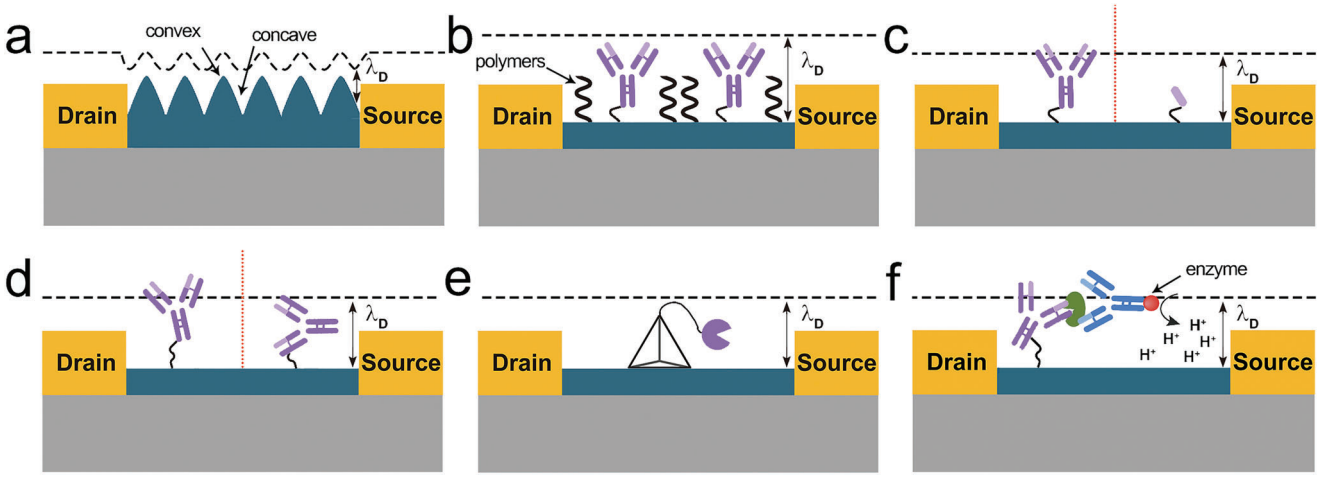

Figure 2. Schematic representation of interface engineering strategies in FET-based electrical devices for biosensing. a) Construction of nanostructured semiconductor channels. b) Surface modification of channel materials. c) Structural design of antibodies. d) Orientation regulation of antibodies. e) Design of nucleic acid probes. f) Conjugation of enzymatic reactions.

following section, the above-mentioned two approaches to overcoming the limitation of Debye screening were comprehensively introduced.

2.1.1. Construction of Nanostructured Channel Materials

The construction of nanostructured channel materials has been proven to regulate the distribution of ions on the sensing interface and enlarge the Debye length of FET biosensors. As early as 2014, Shoorideh et al. first observed an enhanced sensitivity in concave corner regions and disappointed sensing performance in convex regions of silicon nanowires (SiNWs) FET biosensors. The improved sensitivity in corner regions might be attributed to the reduced Debye screening effect that allows a larger potential change when conjugated with biomolecules.[62] In 2020, by molecular dynamics simulations and experiments, Hwang et al. confirmed the decreased Debye screening effect and an extended Debye length in the concave regions of a crumpled graphene-based FET biosensor (**Figure 3**a). The initial graphene was first transferred onto a polystyrene substrate, and with the thermally induced transformation of the polystyrene substrate, a crumpled nanostructure of graphene was achieved. The convex regions of crumpled graphene would form electrical "hot spots" and attract counter ions adsorbed on their surface. Consequently, the ions adsorption at the concave regions would be decreased and the Debye length of crumpled graphene was enlarged.[34] Except for the increased Debye length, the special nanostructure endows the graphene semiconductor channel with the merits of an opened bandgap and enhanced on/off ratio, resulting in an ultrahigh sensitivity for DNA identification. The limit of detection (LOD), refers to a metric for quantitative description

Table 1. Comparison of interface-engineered FET biosensing devices.

Sensing materials	Biorecognition elements	Analytes	Interface engineering methods	Performance	Refs.
Graphene	ssDNA	DNA	Crumpled graphene	20 aM	[34]
Graphene	Aptamer	Con A	Graphene–Nanowire hybrid nanostructures	Robust stability	[50]
Graphene	Aptamer	PSA	PEG modification	Below 1 nM	[51]
Graphene	ssDNA	Viral RNA	TDFs scaffold with flexible ssDNA cantilever	0.025 copies L^{-1}, long-term stability	[52]
Graphene	Cysteamine	•OH	Inner-cutting strategy	≈1 nM, high stability	[53]
MoS_2	ssDNA	Genome	Au NPs deposition	100 aM, high stability	[54]
MoS_2	Aptamer	Cortisol	Nanoporous MoS_2	1 ag mL^{-1}	[55]
Si-nanoribbons	Biotin	Avidin	Lipid membrane coating	100 pM	[56]
PEDOT:PSS	Spike protein	Nanobody	Antibody engineering	0.28 fM, high stability	[57]
PEDOT:PSS	MIPs	Cortisol	Artificial bioreceptor	1 pg mL^{-1}, high chemical and physical stability	[58]
IGZO	Antibody	NMP22	Glutaraldehyde crosslinking	32 ag mL^{-1}, high stability	[59]

ssDNA: single-strand DNA, Con A: *Concanavalin* A, PSA: prostate-specific antigen, PEG: polyethylene glycol, TDFs: DNA tetrahedral frameworks, •OH: hydroxyl radical, MoS_2: molybdenum disulfide, Au NPs: gold nanoparticles, PEDOT:PSS: poly(3,4-ethylene dioxythiophene) doped with poly(styrene sulfonate), NMP22: nuclear matrix protein 22, MIPs: molecularly imprinted polymers.

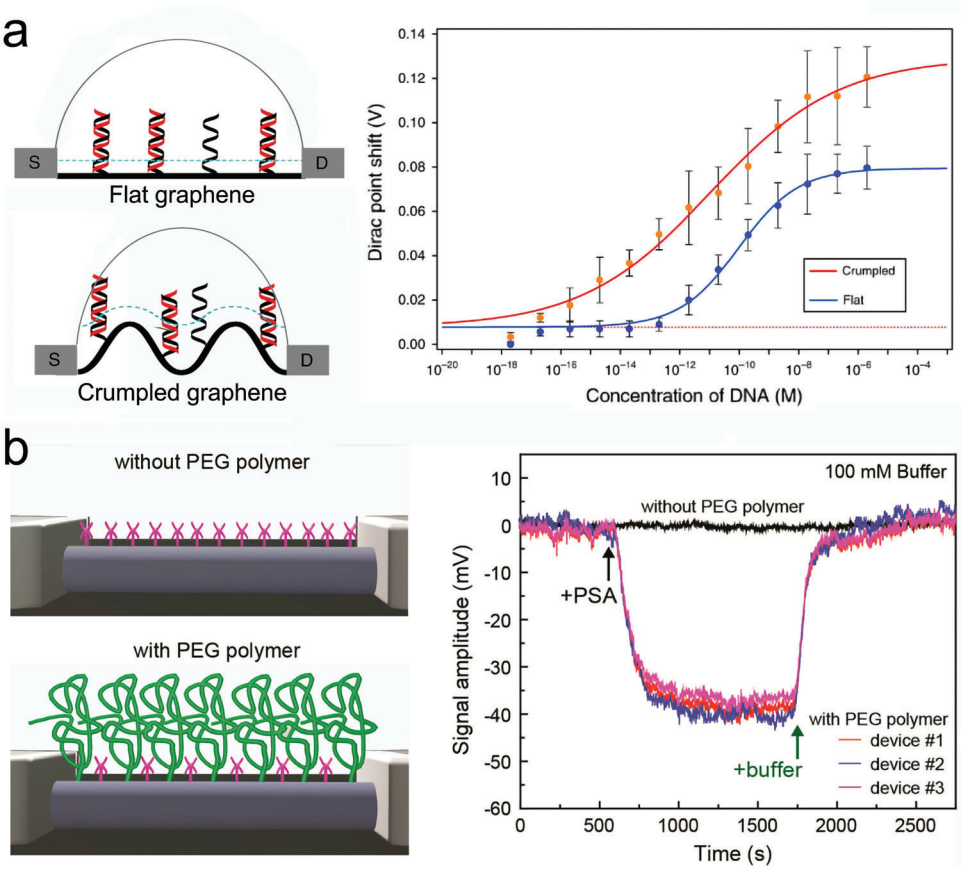

Figure 3. Interface engineering in sensing materials by developing nanostructured sensing interface and surface modification with polymers. a) Schematic of the flat and crumpled GFET biosensors for the detection of nucleic acids. Reproduced with permission.[34] Copyright 2020, Springer Nature. b) Schematic illustration and biosensing performance of a SiNW FET biosensor without and with polymer modification on the sensing interface. Reproduced with permission.[81] Copyright 2015, American Chemical Society.

of the minimal concentration that can be detected, reached as low as 600 zM in buffer solutions and 20 aM in human serum samples.[33,63,64] Recently, Sen et al. presented a precise and sensitive FET-based platform based on nanoporous MoS_2 sensing channel surrounded by non-planar Al_2O_3 for the detection of PSA with a LOD of 1 fg mL^{-1}. The ultra-thin Al_2O_3 dielectric layer along the nanoporous MoS_2 surface increased the interaction interfaces between biorecognition elements and biomolecules, as well as preventing the surface degradation of the MoS_2, thus improving the stability and reproducibility of biosensors. Remarkably, the concave regions of Al_2O_3 dielectric layer along the nanoporous structure of MoS_2 channel might contribute to the high sensitivity of the nanoporous MoS_2 FET, which provides another strategy for the development of nanostructured-interface FET biosensing devices.[65] It could be concluded that the nanostructure of sensing materials plays an essential part in the sensing capability of FET biosensors. Future investigations are required to explore the universality of this strategy on other types of semiconductor channel materials and deeply reveal the underlying mechanisms.

In addition to regulating the Debye length, the inclusion of nanostructure could also improve the surface-to-volume ratio of sensing materials and offer sufficient sites for the efficient interaction between sensing interfaces and biomolecules.[66–70] The representative preparation methods to construct nanostructured interfaces include conducting polymer film electro-polymerization, vapor deposition polymerization (VDP), nanoparticle deposition, and plasma etching.[54,71–73] Notably, by introducing nanoparticles to sensing interfaces, an improved surface area is obtained and abundant functional sites are provided for biorecognition elements immobilization.[74–76] Additionally, the electron transfer efficiency between biomolecules and semiconductor channels was improved due to the excellent conductivity of metallic nanoparticles, enabling reduced detection limit (≈aM level) of FET biosensors.[55,77–79]

2.1.2. Surface Modification of Channel Materials

The inclusion of a permeable polymer layer on the sensing interface to modulate the Debye length of FET biosensors has also attracted wide interest from researchers.[80] Gao's group first observed promoted detection performance in polyethylene glycol (PEG) modified SiNWs FET biosensors (Figure 3b).[81] The SiNWs FET biosensors with PEG modification could

sensitively detect 6 nM prostate-specific antigen (PSA) in electrolyte solutions with phosphate buffer (PB) concentrations as high as 150 mM in which the theoretical Debye length is only ≈0.54 nm. By contrast, similar FET biosensors without PEG modification only exhibit detectable signals when the concentration of electrolyte solutions is below 10 mM (theoretical Debye length is 2.2 nm). They demonstrated that the enhanced sensing performance is attributed to the change of dielectric constant that results in the modulation of Debye length and narrowing of the distance between targets and sensing interfaces after PEG functionalization. Very recently, our group proposed the design of an interfacial polymer-engineered FET biosensor for the efficient identification of viral antigens in saliva samples. With two kinds of monomers polymerizing on the channel material, we fabricated polydopamine and polypyrrole functionalized FET biosensors, respectively. As expected, the distance between targets and the sensing interface was shortened by the inclusion of a polymer functionalization layer, which effectively overcomes the limitation of the Debye screening effect in a biological environment. The developed interfacial polymer-engineered FET biosensor shows remarkable performance in pathogen antigen identification with a LOD down to 4.6 fg mL^{-1} in saliva, as well as excellent anti-fouling capability.[82] The deposition of the polymer layer provides a universal strategy to construct high-performance FET biosensors for practical biological environment detection.

In addition, by utilizing the abundant functional groups on the side branches of polymers, an increased functionalization density of biorecognition elements could be achieved.[83] For instance, Hess et al. developed a polymer-modified graphene FET biosensor (GFET) for the detection of the neurotransmitter acetylcholine. The polymer functionalization layer provided sufficient sites for acetylcholinesterase modification. At the same time, the introduction of crystal defects in the graphene sensing channels caused by direct modification can be effectively avoided.[84] Moreover, the modified polymer could serve as a blocking layer to prevent nonspecific adsorption, thus enabling the long-term and continuous detection of biomolecules in the complicated biological environment.[29,85]

Except for the modification with polymers, lipid layers were also employed to assemble on FET biosensors to overcome the Debye screening effect.[86,87] Attributed to the fluidity and flexibility of the biomimetic lipid layer, the morphology and affinity of bioreceptors could be well preserved.[88,89] More importantly, some research works reflect that the Debye length might be extended after the functionalization of lipid layer. This is due to the fact that the hydrophobic region of the lipid layer contains almost no charged ions and thus contributes less to Debye screening.[90] For example, by coating sensing interfaces with natural red blood cell membranes, Gong et al. proposed a lipid layer-modified FET nanobiosensor to achieve sensitive and selective determination of broad-spectrum hemolytic toxins with the LOD down to fM level.[91] Later, taking advantage of the spontaneous rupture and self-assembly properties of small unilamellar vesicles, Lee et al. coated the sensing channel with a layer of supported lipid bilayer. Notably, the lipid bilayer-assisted FET platform displays superior biosensing capability with an LOD of 100 pM for avidin in 100 mM buffer solution and excellent reproducibility regardless of environmental ionic conditions. Moreover, the directional alignment of biorecognition elements on the lipid layer contributes to excellent measurement reproducibility.[56] Enormous potentials have been forecasted for lipid layer-assisted FET biosensors in the application of ultra-sensitive analysis under physiological conditions. However, the formation of large-scale and uniform lipid layers on solid-state material remains challenging, which is the demand for more research efforts.

2.2. Interface Engineering of Biorecognition Elements

Biorecognition elements, such as antibodies, nucleic acid probes, and bioreceptors, are the key components of FET biosensors because they work as ligaments to mediate the interactions between target biomolecules and sensing interfaces.[92] Through the reasonable and precise design of biorecognition elements, the distance between target biomolecules conjugated on biorecognition elements and the sensing channel can be effectively shortened, resulting in the evading of the influence derived from the Debye screening effect.[57,93–95] Various approaches for the interface engineering of biorecognition elements have been explored, such as antibody engineering, design of nanostructured nucleic acid probes, and inclusion of enzymatic reactions, which will be concretely discussed in the following section.

2.2.1. Antibody Engineering

Over the past decades, antibody has been proven to be an excellent paradigm for the design of various biosensors with high affinity and specificity.[96] However, due to the large size of full-length antibodies (≈12 nm), antibody-functionalized FET biosensors face the challenge of overcoming the Debye screening effect at high ionic strength. Fortunately, antibodies consist of several functional domains with a diversity of functions, which could be split into diverse fragments with small sizes.[97] Additionally, there are a lot of functional groups in antibodies, such as carboxyl and amino groups. Thus, the molecular orientation of antibodies on the channel material can be regulated by different covalent chemical methods.[98,99] The above two strategies can shorten the height of the antibody molecule on FET biosensors while preserving the recognition capability. In this section, we will discuss these two strategies concerning antibody engineering.

Structural Design of Antibodies: A typical immunoglobulin (IgG) antibody is composed of four polypeptide chains linked by several disulfide bonds. The variable regions (V_L) of antibody includes the antigen recognition domain, which plays a crucial role in the recognizing and binding events between antibodies and antigens.[100,101] As shown in Figure 1b, the recognition domains of full-length antibodies are often excluded out of Debye length on FET sensing interfaces, and the sensitivity of antibody-functionalized FET biosensors is constrained.[40,102] Taking advantage of enzymatic lysis, several antibody fragments with decreased molecule size (<5 nm) and reserved affinity could be obtained, such as $F(ab)_2$, Fab′, and "r lgG" (**Figure 4**a).[25,103–105] These fragments could serve as biorecognition elements to construct high-performance FET biosensors. For instance, Elnathan et al. developed a Fab-functionalized SiNW FET biosensor for the direct detection of biomolecules in untreated serum. The

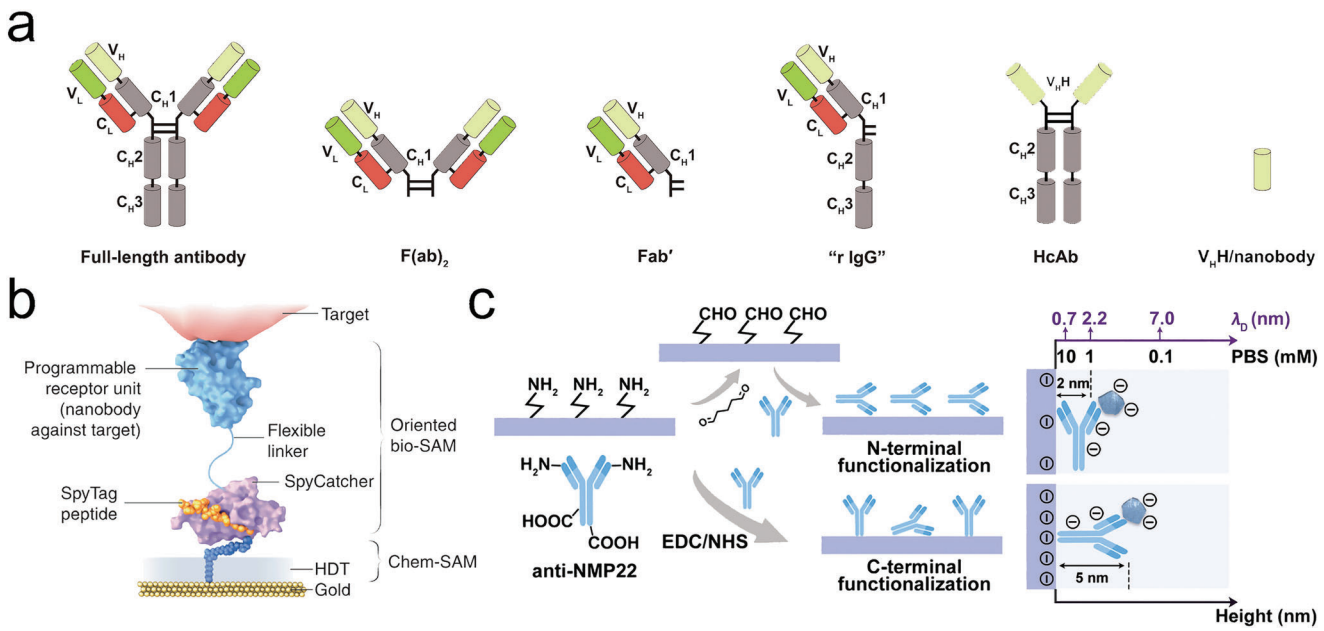

Figure 4. Interface engineering of antibody biorecognition elements. a) The structure of full-length antibodies and antibody fragments, as well as heavy-chain antibodies (hcAb) and nanobodies. Reproduced with permission.[109] Copyright 2018, Wiley-VCH. b) Schematic of the molecular architecture of nanobody-functionalized organic electrochemical transistors (OECT) for virus detection. Reproduced with permission.[57] Copyright 2021, Springer Nature. c) Schematic representation of antibody functionalized IGZO sensing interface by N-terminal and C-terminal functionalization, and the corresponding antibodies height variation on the sensing interface. Reproduced with permission.[59] Copyright 2022, Wiley-VCH.

Fab antibody fragment was obtained by an enzyme Pepsin digestion and cleavage by 2-mercaptoethylamine·HCl. The exploitation of Fab fragments narrowed the distance between target biomolecules and channel materials, thus effectively overcoming the limitation of the Debye screening effect. A highly sensitive cardiac Troponin I (cTnI) identification capability was observed in the Fab-based FET biosensor with an LOD of 1.35 fM (≈50 fg mL^{-1}).[106]

Recently, nanobodies have attracted unprecedented attention for applications in electrical and electrochemical analysis. The invention of nanobody was inspired by an exceptional class of IgG observed in the sera of *Camelidae*, which was defined as heavy-chain antibodies (hcAb).[107,108] Different from the full-length antibodies extracted from mammals, hcAb only contains an antigen-binding unit that was reduced to a single variable domain (V_HH) on the N-terminal of heavy chains (Figure 4a). By isolating the single domain regions from hcAb, recombinant V_HH with higher specificity and affinity could be obtained and named as nanobodies.[109] The small size and reserved binding affinity of nanobodies make them highly suitable for the development of ultrasensitive FET biosensors.[110] For instance, Guo et al. demonstrated the design of nanobody-functionalized OECT with operational and environmental stability and achieved the rapid quantification of viral proteins at single-molecule levels in biological media (Figure 4b). The LOD of the fabricated nanobody-functionalized FET biosensor is 1.2 aM in saliva, which provides a powerful platform for trace biomolecule detection in biological media.[57] Despite the remarkable sensing capability of nanobody-functionalized FET biosensors, little work has been conducted to date due to the high cost of isolation and fabrication of nanobodies. Moreover, the activity of recombinant antibodies in vitro is generally less energetic than the natural antibody in organisms.[111,112] With great advances in life science and molecular biology, it is believed that engineered antibodies will undoubtedly play crucial roles in the exploitation of high-performance biosensors.

Orientation Regulation of Antibody: Besides the isolation of antibody fragments, the regulation of the orientation of antibodies is considered a promising alternative to enhance the sensitivity and stability of biosensors.[42] The orientation of antibodies could be regulated by different functionalization manners.[97,113] For example, considering the functional group differences in the N- and C-terminal of antibodies, our group has employed two covalent modification methods to regulate the orientation of antibody molecules on the sensing interface. Specifically, glutaraldehyde (GA) could conjugate the N-terminal of antibody on the (3-Aminopropyl)triethoxysilane treated sensing interface, and the 1-ethyl-3-(3-dimethyl aminopropyl)carbodiimide/*N*-hydroxysuccinimide (EDC/NHS) activation would result in the binding of C-terminal of antibody. As shown in Figure 4c, the N-terminal functionalization method shortened the distance between target biomolecules and the channel material for ≈3 nm.[59] For 10^{-16} g mL^{-1} NMP22 at a low ionic strength solution (0.1 mM PBS), the current responses of N-terminal and C-terminal functionalized FET biosensors are 26% and 20% respectively, which is relatively close. It might be attributed to the long Debye length (≈7.0 nm) where the majority of charges on NMP22 molecular were located. Whereas, along with the increase of ionic strength from 0.1 mM PBS to 10 mM PBS corresponding to a Debye length of 0.7 nm, the current response of N-terminal functionalized IGZO FET biosensor (15.7%) is much higher than that of C-terminal functionalization (5.6%). In addition, the

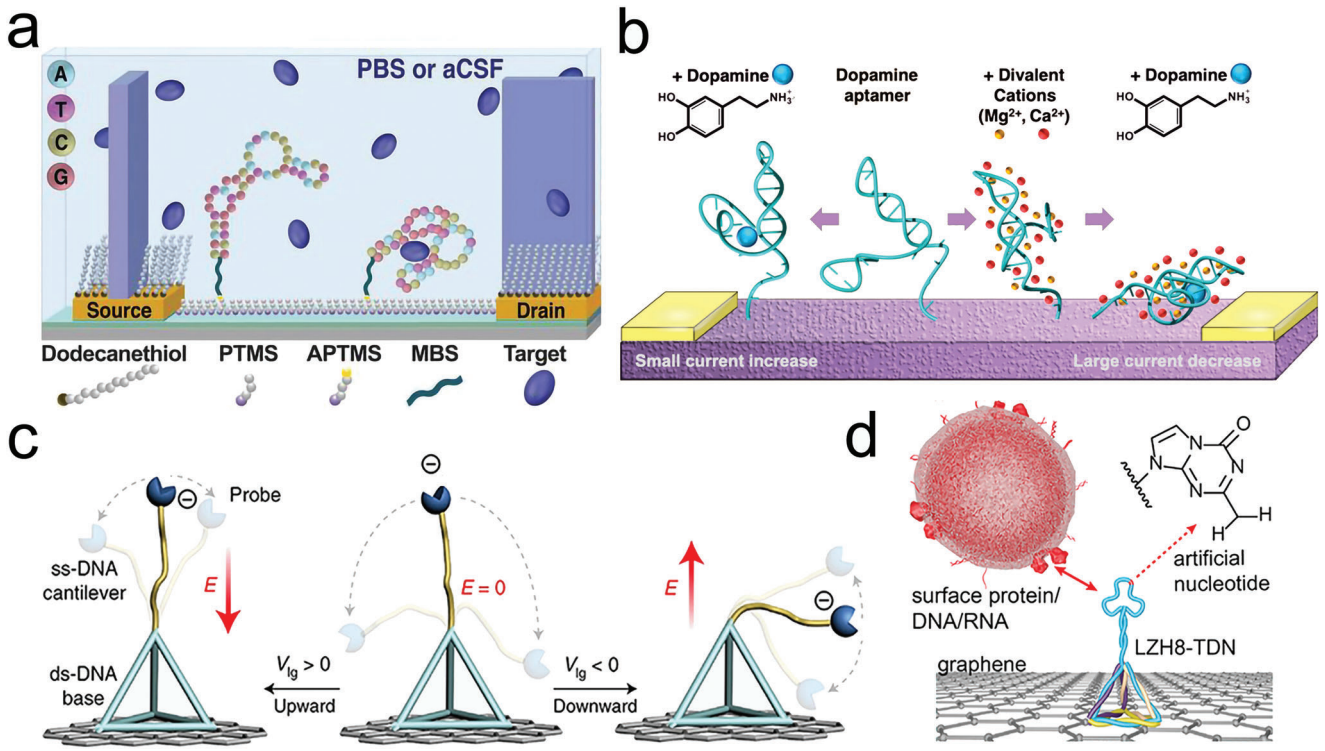

Figure 5. Interface engineering of biorecognition elements by constructing nanostructured nucleic acid probes. a) Schematic of an aptamer functionalized FET biosensor and conformational change of aptamers after binding with targets. Reproduced with permission.[41] Copyright 2018, American Association for the Advancement of Science. b) Schematic diagram of sensing performance for aptamer functionalized FET biosensors with or without the modulation of divalent cations. Reproduced with permission.[49] Copyright 2021, American Chemical Society. c) Schematic illustration of tetrahedral structured nucleic acid probes modified on graphene and its electrostatic actuation under electric field bias. Reproduced with permission.[5] Copyright 2022, Springer Nature. d) Schematic illustration of a GFET biosensor based on a tetrahedral nucleic acid scaffold and artificial nucleotides reformed aptamers for exosome analysis. Reproduced with permission.[121] Copyright 2022, American Chemical Society.

N-terminal functionalized biosensors could reduce the influence of ionic strength on the detection capability and exhibit excellent reproducibility for patient urine sample analysis. These features and advantages convince us that the regulation of antibody orientation offers an efficient strategy to minimize the occupied length of antibodies and enables more charges located within Debye length.

2.2.2. Design of Nucleic Acid Probes

Compared to the engineering process of antibodies, the structural design and synthesis of nucleic acid probes appear to be easier and more attractive. As a unique nucleic acid probe with specific stem-loop structures, aptamer features numerous advantages including small size, favorable structure designability, and high affinity.[30,114] Till now, aptamers have been widely employed to recognize and bind with diverse molecular species such as ions, small molecules, proteins, peptides, bacteria, viruses, and cells.[35,64,115,116] Benefiting from the above-mentioned merits, aptamers hold promising potential in developing highly sensitive FET biosensors for point-of-care diagnosis.[5,117] Compared to antibodies, the significantly reduced dimension of aptamers enables a decreased spacing distance between targets and sensing interfaces, perfectly overcoming the limitation of the Debye screening effect. Nakatsuka et al. designed small-sized aptamers and further demonstrated the conformational changes of aptamers after binding with biomolecules, which shorten the distance between targets and sensing channels (**Figure 5**a). Moreover, stable concentration-dependent conductance responses were produced during continuous exposure to brain tissue for 4 h, demonstrating the promising stability of the aptamer-FET biosensor.[41] In addition to the structural arrangements of aptamers after the binding of target biomolecules, the inclusion of ions could also induce the conformational change of aptamers due to the presence of abundant negative charges in phosphate backbones. A recent report from Nakatsuka's group indicates that the divalent cations, such as Mg^{2+} and Ca^{2+}, are capable of assisting the conformational change of dopamine-specific aptamers and shortening the distance between dopamine and the sensing channel (Figure 5b).[49] Consequently, the developed FET biosensors are highly sensitive in the detection of dopamine with a low LOD of 10 fM. Since cations would compromise the biorecognition and binding affinity of aptamers, the enhanced detection ability of aptamer functionalized FET biosensors through the mediation of divalent cations has been only observed in a few reports.

As a type of frame nucleic acids, DNA tetrahedral frameworks (TDFs) provide a versatile and stable scaffold for the immobilization of biorecognition elements, which have attracted

great interest in the field of nucleic acid analysis.[5,118–121] Wang et al. reported the electric field-modulated dynamic swing of a flexible cantilever fixed on a stiff TDF scaffold, which helps to controllably regulate the distance between targets and sensing channels. Specifically, once the target is bound with biorecognition elements, the target will move toward the sensing channel along with the swing of the flexible cantilever under the effect of an electrical field. Eventually, the distance between the targets and sensing interfaces is decreased, resulting in a significant change in FET channel current (Figure 5c). Based on these principles, they developed an ultrasensitive sensing platform for unamplified viral RNA and ion detection. The LOD of the developed ultrasensitive FET devices is capable of detecting viral RNA down to 0.02 copies μL^{-1} in nasopharyngeal swab samples, which is several orders of magnitude lower than other reported assays (6 copies μL^{-1}).[5] Further, by direct assembly of two TDFs, Wu et al. proposed the design of a triple-probe TDF dimer-functionalized GFET device. Attributed to the strengthened recognition and capture efficiency originating from three probes and TDF scaffold, the GFET exhibited a significantly improved sensitivity and selectivity for viral RNA determination with detectable concentration down to 0.025–0.05 copies μL^{-1}.[120] Since the TDFs exhibit inherent dimensions, the appropriate regulation of spacing distance between TDFs could avoid the aggregation and entanglement of nucleic acid probes and further improve the detection performance of FET biosensors.[38,119] Recently, through the incorporation of aptamers and TDFs scaffold, Chen et al. presented an exemplification of an artificial-modified aptamer FET biosensor applied for hepatoma exosome determination. The artificial-modified aptamer includes two components, an artificial nucleotide-modified aptamer recognition unit and a TDFs scaffold (Figure 5d). The introduction of artificial nucleotides considerably enriches the diversity of aptamer structures. Moreover, with the assistance of the TDFs scaffold, the conformational changes of aptamers could be further amplified, which helps to improve the sensitivity and stability of the aptamer-based detection platform (with a LOD down to 242 particles mL^{-1}).[121] Additionally, Ren et al. demonstrated the design of a bionic biomarker entrapment system (BioES) based on a multi-body tetrahedral DNA probe and realized the sensitive detection of estrogen receptor (ERβ) with an LOD of 6.74 aM. The multi-body BioES possessed a TDF scaffold and a flexible cantilever composed of a double-headed probe. The multisite recognition domains enhanced the binding efficiency of the recognition element. With the help of the TDF scaffold, the excellent sensitivity and reproducibility of BioES were also achieved.[122]

2.2.3. Conjugation of Enzymatic Reactions

As fundamental working laws of biosystems, enzymatic reactions have validated their powerful capability in biosensor development.[123] Compared to FET biosensors on the basis of receptor-target specific recognitions, enzyme-based FET biosensors display much higher sensitivity and specificity. This may be attributed to the effective electron transfer, as well as doping or electrostatic effects originating from the easily diffused small metabolites, such as H^+. Therefore, enzyme-based FET biosensors could escape from the influence of Debye screening even in high ionic strength solutions (Figure 1b).[124–128] Representatively, taking a combination of the OECT based on electron-transporting (n-type) organic semiconductor and redox enzymes, Inal et al. designed a rapid, selective, and sensitive metabolite biosensor for the detection of lactate. The electrons triggered by the enzymatic reaction could be directly accepted by n-type polymers along with a significant signal response in the OECT equipment, further enlarging the advantages of OECT in signal amplification.[129] Later, based on the previous investigation, Inal's group further developed redox enzyme-coupled self-powered OECT biosensors for the determination of glucose in physiological conditions. Attractively, the self-powered OECT biosensors exhibited over month-long stability in terms of power output and glucose detection, showing great potential in autonomous biosensing in biological fluids.[130]

Up to now, enzyme-anchored FET biosensors have been employed in the detection of small molecules at fM level attributed to the amplification effect of enzyme catalysis, including glucose,[124] limonene,[131] urea,[132] lactate,[133] etc. For the non-enzymatic targets, enzyme-based FET biosensors have been extended to detect a variety of proteins through sandwich immunorecognitions, including human immunoglobulin (HIgG),[134] epidermal growth factor receptor,[135] human epidermal growth factor receptor 2 (HER2),[136] cTnI and even microRNA.[137] Owing to the enormous progress in enzyme-based FET biosensors, some researchers are trying to integrate the enzyme-based FET biosensors on a miniaturized wearable or in situ monitoring platform.[124,138] However, owing to the inherent limitations in enzymatic activity, uncontrolled enzymatic reaction, and complex operation, the practical applications of FET biosensors based on enzymatic chemical signal amplification are still challenging, especially for sandwich immunoassay FET biosensing. And the exploitation of biomimetic enzyme systems in enzyme-based FET biosensors might be a satisfactory solution.

2.2.4. Exploitation of New Recognition Elements

Besides the above-mentioned approaches for interface engineering in biorecognition elements, the exploitation of new recognition elements has attracted an increasing number of interests. A long time ago, many researchers devoted their attention to developing new artificial recognition units with the capability of identifying and binding with targets. Inspired by natural biomolecules (nucleic acids and antibodies), peptide nucleic acids (PNAs) and molecularly imprinted polymers (MIPs) were successively exploited and utilized in FET-based electronic biosensing devices. Consisting of amino acids rather than nucleic acids, PNA possessed a neutral peptide backbone and could specifically bind with DNA or RNA.[139,140] Whereas, different from DNA probes, PNA exhibits much higher sequence-specific affinity and stability. This may be attributed to the rigid amido bonds of PNA, as well as the high flexibility of the aminoethyl linkers and intramolecular hydrogen bonding.[141] In addition, the neutral peptide backbone of PNA replaces the negatively charged deoxyribose phosphate backbone in DNA, which leads

to the fact that the electrostatic repulsion between the hybridized strands and the electrostatic influence on sensing interfaces during the wiggle of probes are significantly weakened or even eliminated.[142] Thus, PNA-based FET biosensor often displays a reduced background signal and a higher sensitivity in nucleic acid determination. For example, Cai et al. developed a GFET biosensor based on PNA–DNA hybridization for ultrasensitive and highly specific DNA profiling. Except for a low LOD (≈100 fM), the developed GFET biosensor shows the ability to distinguish the target sequence from one-base mismatched DNA.[143]

Early in the 1990s, MIPs had been exploited and applied in FET-based electrical detection platforms.[144] Compared to antibodies and bioreceptors, MIP-based FET biosensors feature credible selectivity, durability, cost-effectiveness, and stability under different environmental conditions.[145] Notably, considering the distinctive polymer dielectric properties and the biorecognition pockets deep into ontology, the capability of escaping from the Debye screening effect might be demonstrated by MIP-based FET biosensors. For instance, by photopolymerization of methyl methacrylate under ultraviolet irradiation, Parlak et al. fabricated a MIP-based wearable FET diagnostics platform for stable and selective monitoring of cortisol in sweats.[58] The specific affinity of MIPs to the selected "template" molecules depends on the cavities in the polymer matrix during the fabrication process. In order to further improve the selectivity of MIPs, attempts were made to change the density of crosslinker and rationally design monomer composition, aiming at introducing or enhancing covalent bonds, ionic interactions, electrostatic interactions, and hydrogen bonds between functional monomers and matrix.[146] Tamboli et al. proposed a FET biosensor based on a hybrid synthetic receptor, an aptamer-lined MIP element, for sensitive detection of prostate-specific antigen (PSA) under biological ion concentrations. Owing to the synergistic effect of aptamers and MIP pockets, the biosensor shows an enhanced sensitivity and selectivity compared with traditional aptamer-based FET biosensors.[147] Aside from proteins and small molecules detection, MIPs-based FET biosensing device also displays promising sensing performance and preponderance in chirality analysis.[148] It may be appealing in food and pharmaceutical production as there are only a few portable and scalable biosensors working on highly sensitive detection of single-configuration chiral molecules.

3. Applications of Interface-Engineered FET Biosensors

Taking advantage of the rationally designed sensing interfaces, in combination with the FET units with the characteristics of miniaturization and integration, FET-based electronic devices have been verified with great promise for the identification and real-time monitoring of diverse biomolecules, including nucleic acids, proteins, enzymes, and various small molecules.[17,149–151] In this section, the applications of interface-engineered FET biosensors were summarized, with a focus on their applications in biomarkers in vitro detection, epidemic screening, dynamic stimuli response recording, and applications in wearable/implantable electronics (**Figure 6**, **Table 2**).

3.1. Biomarkers In Vitro Detection

As a class of important biological parameters, biomarkers are normally regarded as indicators of physiological and disease states.[167] In vitro detection of biomarkers has been validated as non-invasive, inexpensive, high throughput, quantifiable, and patient-acceptable assays.[168] FET-based electronic devices feature the merits of portability, low cost, easy operation, as well as rapid and multiplexed detection, which are considered potential competitors for in vitro diagnostics. So far, with elaborately designed sensing interfaces, FET biosensors have been verified in the highly sensitive determination of a lot of biomolecules, such as biomarkers of diabetes (glucose),[169–171] Alzheimer (amyloid-β),[153,172,173] cancer (superoxide dismutase copper chaperone, NMP22 and cytokeratin 8, hepatoma exosomes, HER2, miRNA-21, miRNA-17, miRNA-155),[64,93,121,152,174–178] and inflammation (interleukin-4, interleukin-6, tumor necrosis factor-α, C-reaction protein).[179] For example, inspired by the enlarged Debye length after polymer coating, Janissen et al. presented the design of InP nanowires FET biosensors with biocompatible ethanolamine and PEG derivate coatings for the highly sensitive detection of Chagas disease protein marker (IBMP8-1) with a LOD down to 6 fM (**Figure 7**a).[80] In particular, the diagnosis of diseases based on a single biomarker is not sufficient and often misleading, especially for heterogeneous diseases, such as cancers.[180,181] Recently, our group developed a portable electronic device composed of a multi-channel FET biosensing chip, a device control unit, and an Internet terminal for the simultaneous detection of five bladder tumor-associated proteins in urine samples. The multi-channel biosensing chip is composed of 8 antibody-engineered FET biosensors where the antibodies are anchored on sensing interfaces in a GA-mediated functionalization manner (Figure 7b).[59] The LODs of the integrated urinalysis device to five bladder cancer-associated biomarkers are below 10^{-16} g mL^{-1}, which is significantly lower than those of electrochemical assays and fluorescence assays. Relying on the testing results from clinical patient samples and making use of machine-learning algorithms, the developed portable device is able to discriminate urine samples between bladder patients and healthy individuals. A 95.0% diagnosis accuracy and a 90.0% cancer stages classification accuracy were realized with our developed integrated urinalysis device. Most importantly, the integrated urinalysis device is capable of tracking the status of cancer through recording real-time biomarker signatures before and after surgery. It is believed that the combination of multi-biomarker detection, machine learning, and Internet techniques represents a powerful tool for efficient clinical diagnosis and remote healthcare management.

3.2. Pandemic Disease Screening

The large-scale pandemic of infectious diseases has brought great threats to public health and the global economy.[182,183] Especially in the past three years, the outbreak of Corona Virus Disease 2019 (COVID-19) has caused a total of 76 million infections and 68 million deaths.[184,185] Until now, the variants of SARS-CoV-2 have continued to evolve and spread all over the world.[186,187] It is recognized that the early screening and

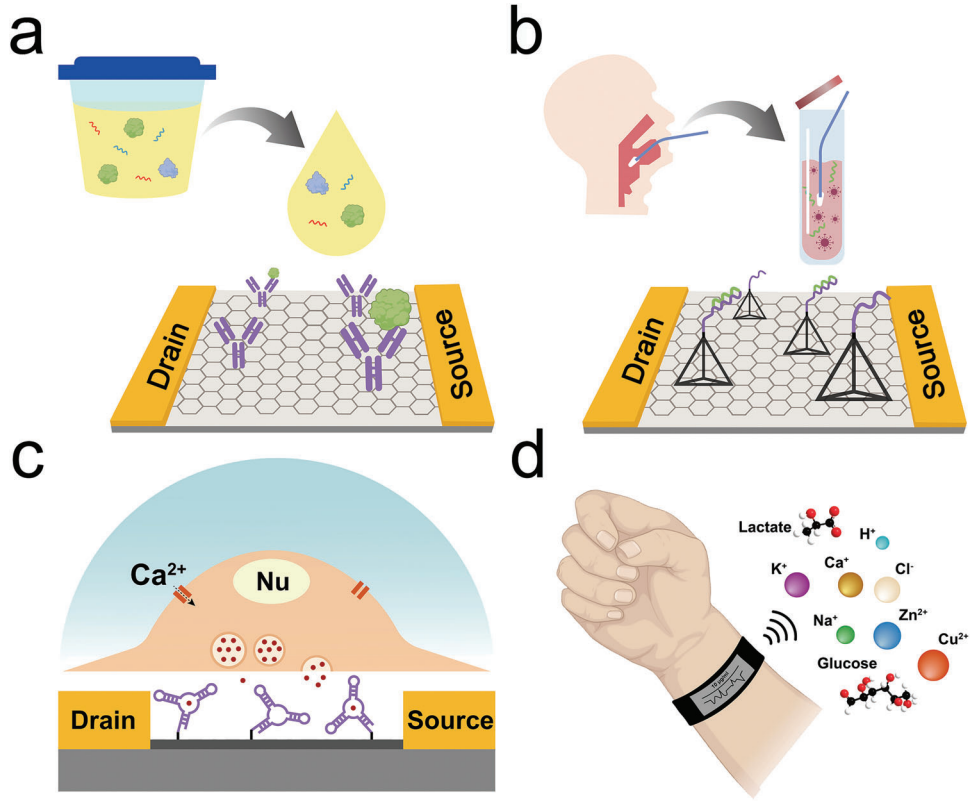

Figure 6. Schematic illustrating the applications of FET-based electronics. a) Biomarkers in vitro detection. b) Epidemic screening. c) Dynamic stimuli responses recording. d) Wearable electronics based on FET biosensors.

isolation of the SARS-CoV-2 infectious could impede the spread of viruses, hence, a large number of detection assays for the identification of SARS-CoV-2 have been developed.[188] The reverse transcription-quantitative polymerase chain reaction and sequencing technologies are gold-standard nucleic acid tests for COVID-19 screening and SARS-CoV-2 variants discrimination. However, these methods require the amplification of target sequences and are time-consuming.[189,190] Additionally, they rely on large-scale equipment and professional personnel, which are unable to meet the requirements of rapid and accurate screening of COVID-19 in the POCT setting.[191,192] Moreover, the viral load is extremely low at the early stages of viral infection and these methods are normally toothless.[193] In comparison, the electronic devices based on interface-engineered FET biosensors provide a sensitive, versatile, rapid, and easy-to-operate tool for the early screening of epidemic diseases.[193–195] An increasing number of FET biosensors with engineered sensing interfaces have been proposed and applied for the screening of SARS-CoV-2 viral, including the whole virus,[196] gene fragments in SARS-CoV-2 genomes (e.g., N gene, E gene, and ORF1ab),[155,197] SARS-CoV-2 proteins (e.g., spike protein and nucleoprotein),[52,57,198] and related antibodies.[40] In order to address the problems of undesired aggregation and entanglement of flexible single-stranded nucleic acid probes on the sensing surface and overcome the limitation of the Debye screening effect, Wei's group developed a series of nanostructured nucleic acid probes for the highly sensitive detection of SARS-CoV-2 viral RNAs. In a representative case, they developed a Y-shaped DNA dual probes (Y-dual probes) modified GFET for viral RNA detection. The Y-dual probes were designed to target two different regions in viral genomes to improve their binding affinity toward viral RNA (**Figure 8**a). More importantly, the Y-dual probe design effectively shortens the distance between the target viral RNA and sensing interface, resulting in the high sensitivity and stable detection of viral RNA with a LOD of 0.03 copy μL^{-1}. The ultralow detection limit is 1–2 orders of magnitude lower than most existing nucleic acid detection assays.[155] Additionally, Wei's group also developed an electric-field-controlled tentacle-shaped DNA probe with a TDF scaffold, realizing the ultra-sensitive detection of SARS-CoV-2 RNA under tunable gate bias. The movement of the cantilevers under a negative gate bias assists the pulling of targets toward sensing interfaces, thus alleviating the influence of the Debye screening effect (Figure 8b). The developed FET biosensor could detect SARS-CoV-2 RNA in less than 4 min with a 100% identification accuracy in nasopharyngeal samples (33 for patients with COVID-19 and 54 for negative controls).[5] Not long before, by regulating the orientations of antibodies, Dai et al. presented the design of a liquid-gated graphene FET biosensors for the detection of trace specific proteins derived from *Mycobacterium tuberculosis*, SARS-CoV-2, and human rhinovirus. Taking the *Staphylococcus aureus Protein A* (SPA) as a linker, the antibodies were upright functionalized on the biosensing channel to achieve active target recognition (Figure 8c). The LOD of the fabricated SPA-modified GFET was down to 5×10^{-16} g mL^{-1}.[156] Although great advances have been made in FET-based pandemic screening, further research about

Table 2. Applications of interface-engineered FET biosensors.

Applications	Analytes	LOD	Response range	Testing condition	Refs.
Biomarkers detection	CCSP-2	100 ag mL^{-1}	100 ag mL^{-1} to 1 μg mL^{-1}	1 × PBS	[152]
	CTxB		0–400 пм	1 × HEPES	[153]
	Lactate		10 μм to 10 мм	1 × PBS	[129]
	Exosomes	242 particles mL^{-1}	6.8×10^2 to 6.8×10^8 particles mL^{-1}	1 × PBS	[121]
	ERβ	6.74 ам	10 фм to 100 рм	1 × Тм buffer	[154]
Pandemic screening	SARS-CoV-2 nucleic acids	0.03 copy μL^{-1}	0.03–500 copy μL^{-1}	Full artificial saliva	[155]
	SARS-CoV-2 IgG	10 рм	10 фм to 100 пм	1 × PBS	[40]
	spike S1 proteins	2.6 ам	5 ам to 5 рм	1 × FBS	[52]
	MPT64	0.5 fg mL^{-1}	0.5 fg mL^{-1} to 0.5 pg mL^{-1}	Serum	[156]
	HPAIV	10^2 EID_{50} mL^{-1}	10^2–10^6 EID_{50} mL^{-1}	1 × FBS	[157]
Dynamic responses recording	Na^+	2.78 пм	10–160 мм	ISF	[60]
	K^+	1 пм	1 пм to 10 μм	10 мм Tris buffer	[158]
	pH	pH 4	pH 4–pH 10	0.1 × PBS	[159]
	Lactate		20–160 мм	M9 buffer	[160]
	NO	1 рм	1 рм to 100 пм	1 × PBS	[161]
Wearable/implantable sensors	MMP-9	0.74 ng mL^{-1}	1–500 ng mL^{-1}	Artificial tears	[162]
	Cortisol	10 pg mL^{-1}	1–40 ng mL^{-1}	Artificial tears	[163]
	Cortisol	1 рм	1 рм to 1 μм	Artificial saliva	[164]
	Serotonin		1 фм to 1 μм	aCSF	[165]
	Dopamine	5 пм	10 пм to 14 μм	aCSF	[166]

CCSP-2: colon cancer secreted protein-2, CTxB: cholera toxin B subunit, MMP-9: matrix metalloproteinase-9, aCSF: artificial cerebrospinal fluid, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, HPAIV: highly pathogenic avian influenza virus, ISF: interstitial fluids, NO: nitric oxide.

the stability and repeatability of FET biosensors is needed to develop a comprehensive and efficient tool for the precise detection of low-abundance infectious disease-associated molecules in real scenarios.

3.3. Dynamic Stimuli Responses Recording

Attributed to the characteristics of rapid response, intrinsic signal amplification, and sensitive biosensing interfaces, the FET-based electronic devices display predominant capability in the dynamic monitoring of cell secretion processes under external stimulation.[199,200] The dynamic responses of cells to environmental and drug stimuli are normally performed as the efflux and internalization of ions, including H^+, Ca^{2+}, and K^+, and the detection of these ions with FET biosensors would be particularly influenced by the Debye screening effect as they could easily diffuse to the sensing interface.[135,201] For example, the injury of the epithelial cell membrane under external stimuli results in the leaking of H^+ and NH_4^+. Hatano et al. developed an H^+ sensing system based on an ion-selective FET biosensor, which could sensitively monitor the pH perturbation during the process of cell membrane injuries and tight junction damages.[202,203] As for neurotransmitter molecules without charges such as dopamine, with the assistance of chemical/enzymatic reactions or conformation change of aptamers on well-designed biosensing interfaces, the presence of these biomolecules could be converted into the change of H^+ concentrations and determined by ions-sensitive FET biosensors. For instance, Pham et al. fabricated a carbon nanotube (CNT)-based FET biosensor for the monitoring of antipsychotic drug effects on cell dopamine release under potassium stimulation. The biosensing interface was functionalized with 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS•) radicals. Depending on the reactions of ABTS• and dopamine, an increased H^+ concentration occurred near the biosensing interface and contributed to a significant current amplitude change of FET biosensors.[204]

Besides, interface-engineered FET biosensors have been applied and validated their performance in the detection of glutamate released from cortical neurons,[158,200] formation status of epithelial cell tight junctions,[202,203] as well as extracellular electron transfer processes.[160] Recently, for rapidly assessing T cells' immune responses to antigens, including seasonal viruses and emergent pandemic coronavirus, Nami et al. proposed the design of a multichannel SiNWs FET biosensor to dynamically monitor extracellular acidification. Extracellular acidification, denoted as increased H^+ concentration of the cellular microenvironment, is typical and direct evidence of T-cell activation. Using the hydroxyl groups on the surface of SiNWs as the recognition element, the H^+ could be easily detected. Meanwhile, the avoidance of external linker molecules eliminates the limitations of the Debye screening effect.[159] The SiNWs FET biosensors provide an emerging strategy to screen the T-cell immune profile, facilitating the development of efficient techniques in vaccine efficacy evaluation. Furthermore, it could be adopted to massively characterize the population-wide immunity efficacy against

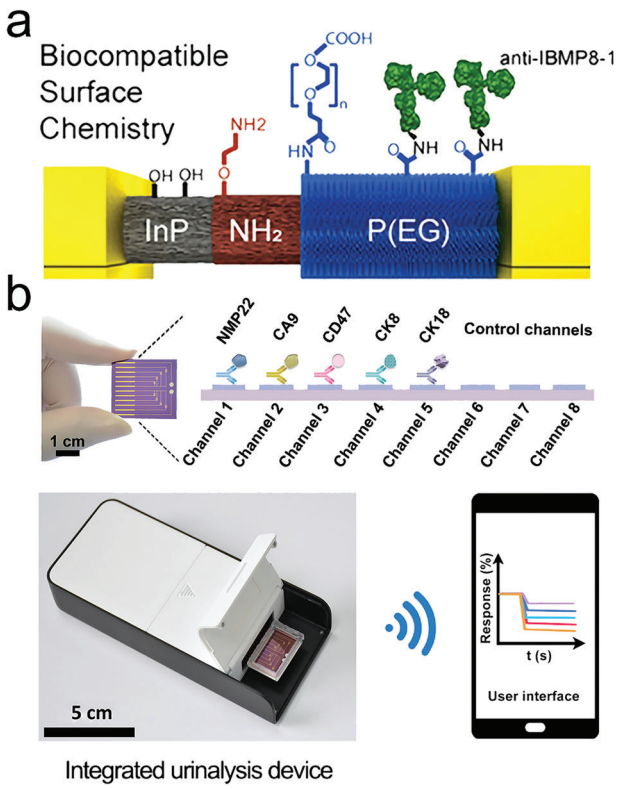

Figure 7. Applications of FET-based electronic devices for the in vitro detection of biomarkers. a) Schematic of the PEG-coated InP FET biosensor and antibody functionalization procedures. Reproduced with permission.[80] Copyright 2017, American Chemical Society. b) Photograph and working principle of the integrated urinalysis device for detecting five bladder cancer-associated proteins in urine samples. Reproduced with permission.[59] Copyright 2022, Wiley-VCH.

emerging pathogens or diseases of interest, such as SARS-CoV-2 and its variants, which contribute to the determination of vaccine formulation. Particularly, cellular metabolism is an extremely complex and interconnected process, and the evaluation of a single parameter is not enough to reliably investigate the detailed cell secretion processes and immune responses. A systematic and comprehensive evaluation is necessary and is of great significance for the development of new vaccines. These demands urge the development of versatile and integrated platforms based on FET electronic devices.

3.4. Wearable and Implantable Monitoring

Health monitoring is experiencing a fast shift from traditional centralized healthcare services to personalized health management, which puts forward urgent demands for equipment applied for real-time monitoring of biomolecules.[205] With remarkable progress in biosensors and integrated techniques, two kinds of health monitoring systems including wearable and implantable electronics have displayed their excellent capability in sustainable personal health management.[20,206] For wearable biosensors, they are often deployed for quantifying biomarkers in various biofluids, including sweat, tears, and interstitial fluid, where the concentration of biomolecules is particularly low.[207,208] Moreover, due to the high ionic strength in biological environments, the Debye screening effect plays a crucial role in the performance of wearable and implantable electronic devices. The interface-engineered FET biosensors exactly meet the requirements of wearable systems, and enormous investigations have proved their ability in biomolecule determination at subnanomolar levels.

Aptamers, with the features of small size and excellent affinity, have been considered ideal candidates for the construction of high-performance FET biosensors with minimized Debye screening, as discussed in Section 2.2.2. For instance, Wang et al. presented the design of an aptamer-functionalized flexible In_2O_3 FET biosensor array for cortisol detection in sweats. Once the cortisol was present in sweat, an obvious electric signal change would be observed attributed to the notable conformational change of aptamers after the binding of cortisol. By integrating their fabricated In_2O_3 FET biosensors with a wearable smartwatch system, a multifunctional wearable platform with the ability of real-time and persistent cortisol sweat monitoring was developed (**Figure 9**a).[164] Except for smartwatches, FET-based electronic wearable systems have been extended to other forms, such as wearable patches,[58,60,209] fabric woven,[210] and smart contact lenses.[211]

In the past three years, Park's group developed a series of soft contact lenses based on FET devices for the wireless detection of cortisol and MMP-9 in tears to achieve the therapy of chronic eye diseases such as ocular surface inflammation (OSI). Ultraviolet ozone was first utilized to pretreat the graphene sensing channel for the introduction of the carboxylate group without extra requirements of linker molecules cross-linking the graphene and biorecognition elements. Then, by utilizing widely acknowledged EDC/NHS chemistry, the biorecognition elements could be efficiently functionalized on the sensing interface with a remarkably shortened spacing distance between target biomolecules and graphene. On the other hand, the $F(ab)_2$ fragments of MMP-9 antibodies were modified on sensing interfaces for efficiently identifying and binding with targets, further shortening the distance between targets and sensing interfaces. The integrated FET-based soft contact lens displayed exceptional sensing sensitivity and stability even after being stored in the air for 16 days, promising great potential in the applications of personalized healthcare.[50,162,163]

Although FETs have been integrated into implantable electronic devices for constantly recording physiological signals, such as electroneurographic and electrocardiographs, little has been reported about their applications in continuous biomolecular measurements to date.[212,213] For currently presented FET-based implantable electronic devices, the deployment of aptamers is also regarded as an effective approach. For example, Zhao et al. fabricated an implantable aptamer functionalized FET neuroprobe to consistently detect serotonin for neurochemical recording by high-throughput microelectromechanical system techniques. The FET neuro-probe is composed of an In_2O_3 sensing channel, aptamer, and Si substrate, displaying excellent sensing capability in neurotransmitter monitoring in vivo with a femtomolar sensitivity (Figure 9b).[165] The poor mechanical deformation ability of neural probes based on rigid substrates remains the primary obstacle for in vivo monitoring, which might cause tissue damage and unexpected immunological responses. A large

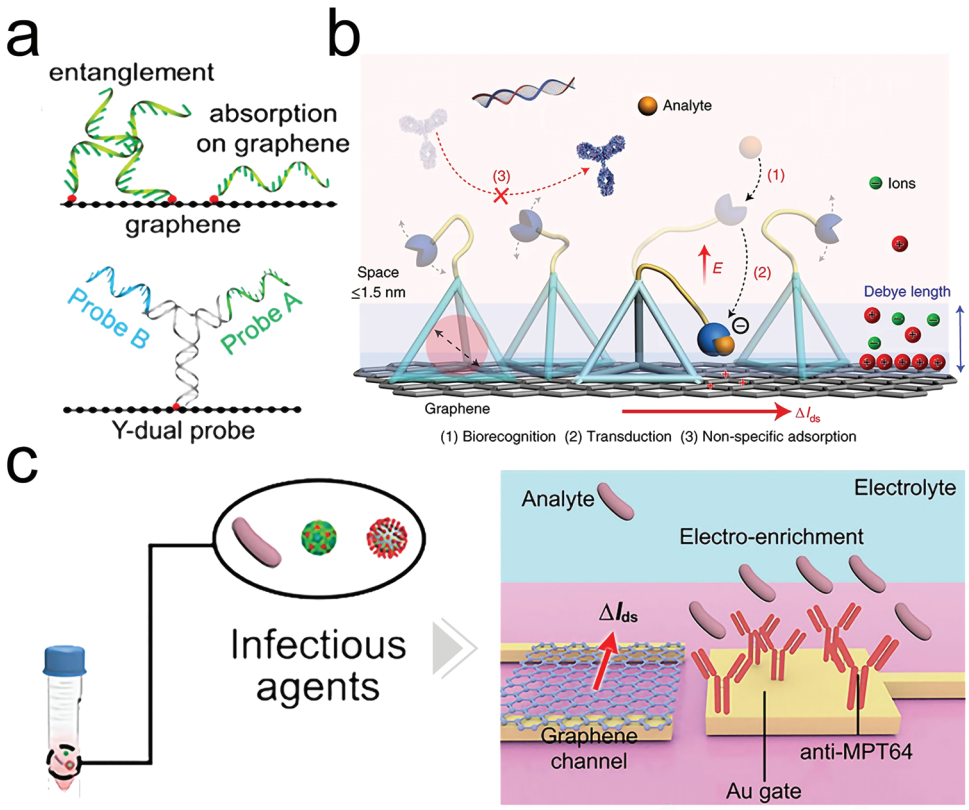

Figure 8. Applications of FET-based electronic devices in pandemic screening. a) Schematic representation of graphene sensing layers modified with single-strand-DNA probes and Y-shaped DNA probes, respectively. Reproduced with permission.[155] Copyright 2021, American Chemical Society. b) Working principle of a tentacle-shaped DNA probe with TDF scaffold under the modulation of electrical field on the sensing interface of a graphene FET biosensor. Reproduced with permission.[5] Copyright 2022, Springer Nature. c) Schematic illustration of the working flow of a liquid-gate GFET biosensor for tuberculosis pandemic screening. Reproduced with permission.[156] Copyright 2023, Wiley-VCH.

variety of efforts have been taken to develop flexible and implantable neural probes, such as flexible polyimide probes.[214] Recently, Gao et al. developed a soft neural probe on the basis of aptamer-functionalized graphene FET biosensor for multiplexed neurochemical monitoring including dopamine, serotonin, norepinephrine, and neuropeptides. Notably, despite incubation in rat cerebrospinal fluid for 96 h, the multiplexed neural probes exhibited the maintained capability for simultaneously monitoring dopamine and serotonin with minimal crosstalk.[215] The further advancement of interface-engineered FET-based wearable and implantable electronic devices is becoming an emerging area of research that deserves deep exploration.

4. Conclusion and Perspective

Interface engineering on FET biosensors provides an effective and universal strategy for developing FET-based electronic devices with excellent performance in sensitivity, specificity, and stability. In this perspective, we summarized the past efforts in biosensing interface design with emphasis on nanostructured

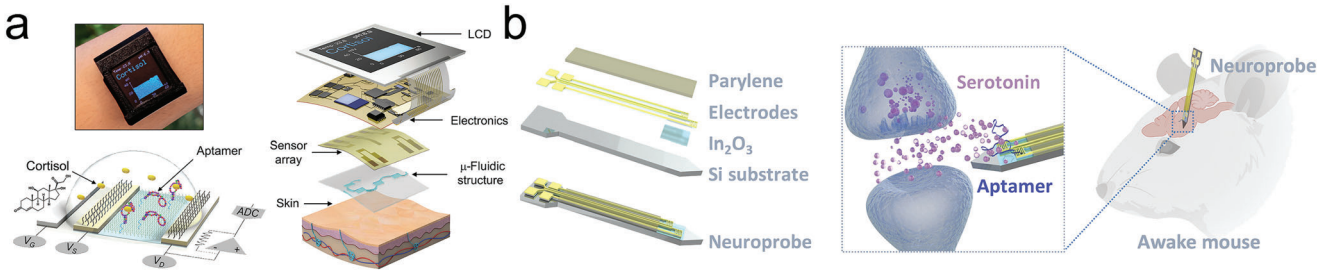

Figure 9. Wearable and implantable FET-based electronic devices. a) Schematic illustration of the structure and detection principle of an aptamer functionalized FET biosensor-based smartwatch. Reproduced with permission.[164] Copyright 2022, American Association for the Advancement of Science. b) Schematic representation of the structure and working principle of an implantable aptamer functionalized FET biosensor-based neuro-probe for femtomolar serotonin detection. Reproduced with permission.[165] Copyright 2021, American Association for the Advancement of Science.

materials construction and interface molecules regulation to achieve high-performance FET biosensors. Further, we summarized the applications of electronic devices based on FET biosensors in biomolecule detection in vitro, such as disease biomarkers and pathogens, as well as consistent health monitoring in wearable or implantable manners. This review provides a comprehensive understanding of current achievements in interface-engineered FET biosensors and will contribute to the design of high-performance electronic devices. Further studies could contain the following aspects.

Firstly, the strategies for biosensing interface regulation are worthy of further investigation. The biosensing interface plays a crucial role in the detection capability of biosensors as they directly determine the biorecognition events between targets and biorecognition elements, especially for compensating the limitation caused by the Debye screening effect. Whereas, till now, there are only a few reports focusing on the optimization of nanostructured sensing interface, as discussed in Section 2.1. The exploration of sensing interfaces with diverse topological structures might contribute to unexpected effects, for example, extended Debye length, enhanced interfacial mass transfer rates, and improved biorecognition efficiency, and eventually result in signal amplification regarding sensitivity and specificity improvement in FET-based devices. The relationship between the topography structure of sensing materials and the Debye screening effect should be deeply explored to seek the optimized structure for efficient biosensing. The nucleic acid probes with tunable nanostructures provide another appealing approach for developing ultra-sensitive FET biosensors, even for non-nucleic acid targets due to the remarkable progress in aptamers. On the other hand, future investigations on nanostructured DNA probes could focus on the engineering of probe arrangement on the biosensing interface to achieve the optimal recognition and binding event. Further minimizing the dimension of the sensing interface may enable the exploitation of much more sensitive biosensors that could be applied to monitor biometric events at concentrations as low as a single molecule. It helps to understand the single biomolecule recognition and combination process.

Secondly, great efforts are expected to be made in wearable and implantable FET-based electronic devices. Current achievements in FET-based wearable and implantable electronic devices are focused on limited physiological index monitoring, for example, K^+, Na^+, NH_4^+, Ca^{2+}, glucose, dopamine, and cortisol in sweat, which fails to satisfy the demands of multiplex biomolecules monitoring in clinical application and personalized healthcare. There remains a long period to achieve consistent biomolecule monitoring in practical biological environments. Moreover, excellent biosensing stability, flexibility, conformability, and biocompatibility are crucial for wearable and implantable biosensing platforms. In the future, for FET-based wearable and implantable electronic devices, the optimization of sensing interfaces, and the design of integrated circuits are crucial. The development of flexible sensing materials and substrates, as well as integrated and packaging techniques are also of vital importance. Fortunately, these demands are able to be realized owing to the development of advanced micro- and nano-electromechanical systems. A stable and continuous fluid collection and transport channel might take another significant role because it ensures the real-time update of analysis media and helps to avoid adverse reactions caused by direct contact with the biological environment. Remarkably, by cooperating with the Internet of Things, wearable and implantable FET-based electronic devices could serve as powerful tools in home healthcare.

Thirdly, most applications of FET biosensors are still limited in laboratories, and challenges remain for their commercial applications from laboratory to market, including robustness, repeatability, reproducibility, scalability, and standardization. Among these factors, robustness, repeatability, and reproducibility are the crucial judgment standards for the development of commercial FET-based electronic devices as they directly determine the precision and accuracy of testing results. As mentioned above, the large batch difference is prominent in FET-based electronic devices, raising worries about the reliability of detection results. Some researchers have made efforts to address the issues of the detection accuracy caused by batch differences through machine learning and complex data processing. Despite the great progress, more efforts are supposed to be taken into the fabrication techniques for FET biosensors, which eventually decide the intrinsic property and sensing performance of biosensors. Furthermore, scalable antifouling technology also provides an effective way to develop stable and reliable FET-based electronic devices. Currently, most antifouling methods are based on self-assembling monolayer and protein blocking. These methods always lead to possibly decreased detection sensitivity and are not reproducible in FET biosensing. Developing uniform antifouling coatings without sacrificing sensitivity is highly demanded for fabricating high-performance FET biosensors. Furthermore, there is a lack of assessment criteria for the standardization of FET biosensors, such as testing conditions, as well as the evaluation methods of sensitivity and specificity. The standardized production processes from materials to products remain a challenge in FET biosensors as the cost of an integrated electronic device based on FET biosensors is still relatively high. Future works could focus on simplifying the configuration of FET biosensors and reducing the relevant cost. Additionally, an integrated electronic device with multiplexed FET biosensing channels will contribute to a significantly elevated testing speed and might be suitable for large-scale and high-throughput screening. Overall, we believe that with more efforts focusing on the rational design of FET sensing interfaces and fabrication techniques, the development and applications of FET-based electronic devices will make strides with a brilliant future.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

biosensing, Debye screening, electronic devices, field-effect transistor, interface engineering

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