

Review

Functionalization Strategies for 2D Material FET Biosensors: Recent Advances and Analytical Applications

Chuangyi Dai¹, Binbin Gao^{1,*} , Zihao Wu¹, Yu Huang¹, Atena Ahmadian¹

¹School of Life Sciences, Jiangsu University, 212013 Zhenjiang, Jiangsu, China

*Correspondence: 2441519538@qq.com (Binbin Gao)

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Abstract

Objective: Field-Effect Transistor (FET) biosensors based on two-dimensional (2D) materials attract considerable attention because of their rapid electrical response, label-free operation, miniaturization potential, and ultrahigh sensitivity. This review systematically summarizes progress in 2D material-based FET biosensors, focusing on biocompatibility, functionalization, and practical applications while critically assessing translational bottlenecks hindering deployment. **Mechanism:** 2D materials such as graphene, MoS₂, and WSe₂ exhibit higher carrier mobility, large surface areas, and tunable surface chemistry, thereby enabling efficient charge transduction upon biomolecular recognition. We examine covalent and noncovalent functionalization approaches, evaluate their effects on interfacial stability, charge transfer efficiency, Debye length limitations, reproducibility, and potential biological risks, and discuss the principles of nucleic acid, protein, peptide, and saccharide sensing enabled by these strategies. **Findings in Brief:** Despite extraordinary sensitivity in idealized buffer systems—with some devices reaching aM or even zM detection limits—practical applications in complex biological environments are severely constrained by the Debye screening effect. In these environments, excess ions in physiological media effectively shield the electrical charges of target biomolecules, attenuating their electrostatic coupling with the sensing channel and thereby drastically reducing the signal magnitude. Additional barriers include nonspecific adsorption, poor device-to-device reproducibility, insufficient long-term stability, and sample pretreatment. Moreover, most biosafety evaluations remain confined to short-term *in vitro* assays, while systematic data on chronic toxicity, biodistribution, and long-term *in vivo* clearance—essential for implantable applications—are still lacking. **Conclusions:** 2D FET biosensors hold promise for next-generation healthcare and precision medicine; however, clinical translation requires a focus shift from ultralow detection limits to stability, reproducibility, biosafety, and real-sample performance. Future work should integrate scalable fabrication, antifouling, the mitigation of the Debye screening effect, and *in vivo* safety tests to bridge academic research and clinical applications.

Keywords: 2D material; FET; biosensor; practical application

1. Introduction

With the development of healthcare monitoring technologies, especially after the novel coronavirus epidemic, the field of biosensors has undergone rapid development, leading to higher performance requirements. In early disease diagnosis and some low-concentration *in vitro* biomarker testing processes, biosensors need to have higher sensitivity, even single-molecule detection capability [1,2,3]. In complex sample detection, it is necessary to achieve the function of simultaneously detecting various biomolecules, which requires biosensors to have multifunctionality and integration [4,5,6,7]. At the same time, personalized medicine and disease monitoring require not only the biocompatibility of the sensor, but also its long-term stability in the process of biomolecular detection [8,9,10,11].

Field-Effect Transistor (FET) biosensors have become a highly suitable platform for advanced biosensing applications because of their preferential interaction with specific biomolecular targets, rapid response characteristics, and ease of miniaturization [12]. FET biosensors can not only realize the fast and real-time detection of biomolecules, but

are also amenable to large-scale production through micro- and nanofabrication technologies, which enables the development of low-cost solutions and portable detection equipment, enabling real-time detection and home medical treatment [13,14,15,16]. Two-dimensional (2D) materials are those with a thickness of only one atom, such as graphene and MoS₂, which exhibit outstanding physical and chemical properties. Recently, the introduction of 2D materials has brought new possibilities for improving the performance of FET biosensors. 2D materials have excellent thermodynamic stability [17], good biocompatibility [18], and excellent electronic storage and transmission properties [19]. These unique attributes of 2D materials can considerably address some limitations of traditional FET biosensors. By combining 2D materials with FET technology, it is expected to develop high-performance biosensors to satisfy the needs across different use cases, and promote the development of biotechnology and engineering [20,21]. The strong sensing capability of 2D material FET biosensors makes them more suitable for single-molecule detection [22,23,24,25]. In recent years, some 2D material FET



biosensors have even achieved aM- and zM-level detection limits under laboratory conditions. However, for many practical biomarkers, clinically relevant concentrations are often significantly higher than these ultralow limit of detection (LOD) values. The label-free detection characteristics and the flexibility of some 2D materials offer a solid basis for the creation of wearable devices and real-time sensing devices [26,27,28,29]. Nevertheless, practical wearable and implantable devices still face challenges such as long-term stability, signal drift, and biofouling under physiological environments. The large effective surface area and easy integration capability of 2D materials make them more suitable for the detection of various components in complex samples [12,23,30]. Multiplex sensing may also introduce signal interference and nonspecific adsorption among adjacent sensing units, thereby increasing the difficulty of practical signal analysis.

Compared to traditional FET biosensors, 2D material FET biosensors can respond sensitively to extremely small electrical signals, while the surface of traditional semiconductors is relatively rough, which can affect the movement of charge carriers in the channel and cause errors in charge carrier migration. 2D materials have better flexibility and can bend or stretch to a certain extent, which is difficult to achieve on traditional silicon-based devices and is associated with higher costs in *in vivo* applications [31,32]. The functionalization methods for traditional FETs are currently relatively mature, but it also faces the problem of weak response signals. In contrast, the functionalization of 2D FET biosensors is relatively straightforward, and combined with their superior capability for electrical signal detection of the material itself, it can achieve high-precision detection while ensuring small errors, which has significant advantages [33,34,35,36]. Although functionalization can improve sensing selectivity and interface stability, it may also change the original surface properties and biological interactions of 2D materials, which could introduce additional biosafety risks. At the same time, many current studies still rely on simulated physiological environments, such as artificial biofluids, for real-sample detection. These systems still differ considerably from real biological samples, and the sensing performance is often lower than that obtained in buffer solutions, indicating that practical detection in complex physiological environments remains challenging.

While excellent reviews have covered 2D material FET biosensors from materials (e.g., graphene, MoS₂), applications (wearable, point-of-care), or device perspectives, the present review offers three distinctive contributions embedded in our analysis. First, we integrate biosafety assessment with functionalization design (Section 1, Table 1, Ref. [37,38,39,40,41,42,43,44,45,46,47,48,49,50,51]): rather than treating cytotoxicity as an isolated topic, we explicitly link the toxicity profiles of various 2D materials to the choice of surface functionalization (e.g., PEG, polysarcosine) that can mitigate immune responses and improve

long-term stability. Second, we introduce a mechanism-driven comparative framework for covalent vs. non-covalent functionalization (Sections 3.6 and 4.5), evaluating them across six key parameters—charge transfer efficiency, signal stability, Debye screening mitigation, reproducibility, scalability, and clinical applicability – a critical comparison absent from previous reviews. Third, we offer a critical reassessment of sensitivity metrics (Section 5, Table 2, Ref. [24,52,53,54,55,56,57,58,59,60,61,62,63,64], Table 3, Ref. [20,65,66,67,68,69,70,71,72,73,74,75,76], Table 4, Ref. [77,78,79,80,81,82]), arguing that the field's obsession with ultralow aM/zM detection limits often overlooks more pressing translational barriers, such as performance degradation in real biological samples, device-to-device variation, and long-term reliability. Collectively, these features render this review not merely a summary, but a practical decision-making guide for researchers advancing from buffer-based demonstrations toward clinical, wearable, and implantable applications.

2. Biocompatibility of 2D Materials

The application of 2D materials in biosensors benefits from their high electrical and mechanical properties. In actual biological detection processes, the biocompatibility of 2D materials should also be evaluated to ensure their safety during the detection process and the stability of the device itself. Especially for wearable and implantable biosensors, factors including cytotoxicity, immune responses, biodegradation, and long-term stability under physiological conditions should be considered during material selection and device design [83,84]. Although many 2D materials exhibit relatively good biocompatibility in short-term studies, their long-term biological effects and potential biosafety risks in complex physiological environments still require further investigation. Therefore, this section mainly discusses the cytotoxicity, immune response, and long-term stability of 2D materials in biological environments.

2.1 Cytotoxicity

Cytotoxicity is a key indicator for evaluating the safety and applicability of 2D materials in biological or *in vivo* sensing environments. It is crucial to select suitable 2D materials for biomolecular detection in different environments, to minimize the potential harm from detection devices and procedures to living organisms. Studies have shown that the cytotoxicity of 2D materials is closely related to the chemical makeup, surface properties, and size [85].

Graphene and its derivatives: at present, the cytotoxicity of graphene and its derivatives (such as graphene oxide) is mainly determined by cell viability and cell membrane integrity [37]. Although graphene generally shows good cell compatibility at low concentrations, it may cause cell membrane damage and oxidative stress responses at high concentrations or after prolonged exposure [38,39]. Graphene

Table 1. Cytotoxicity of representative 2D materials and their main mechanisms.

2D Material	Toxicity Level	Main Mechanisms (Brief)	References
Graphene and its derivatives	Low	Concentration-dependent membrane damage and ROS generation; high dose/exposure induces DNA strand breaks and genome instability.	[37,38,39,40,41]
TMDs	Low	Induce ferroptosis; interact with α -helical proteins causing secondary-structure disruption and reduced cell activity.	[42,43,44]
Diselenides	Medium	Se participates in redox reactions and may release free Se, causing oxidative damage, DNA breaks, and gene mutations.	[45,46]
BP	High	Easily degraded; produces excessive ROS; induces lipid peroxidation and cell death; requires surface stabilization.	[47,48]
MXenes	Medium	High concentrations cause autophagy dysfunction; negatively affect embryonic development and angiogenesis.	[49,50]
h-BN	Low	Generally biocompatible; high doses induce ROS, leading to structural alterations in proteins and DNA.	[51]

2D, Two-dimensional; ROS, reactive oxygen species; TMD, transition metal disulfide; BP, black phosphorus; h-BN, hexagonal boron nitride.

and its derivatives may also have an impact on DNA structure, thereby potentially affecting sensing stability and biological safety. Graphene can induce DNA damage and ROS-mediated cleavage, which may lead to genomic instability and cell apoptosis [37,40,41].

Transition metal disulfides (TMDs): such as MoS₂ and WS₂, which have relatively low chemical activity and usually exhibit low cytotoxicity, are suitable for biosensor development and biomedicine [42]. Studies have shown that MoS₂ and WS₂ nanosheets induce ferroptosis in Bronchial Epithelium transformed with Ad12-SV40 2B (BEAS-2B) epithelial cells and Tohoku Hospital Pediatrics-1 (THP-1) macrophages, while surface passivation with methanol or sulfide can reduce cytotoxicity [43]. MoS₂ nanosheets can interact with proteins, such as α -helical peptides, disrupting their secondary structure, resulting in loss of protein function and changes in cell activity [44].

Diselenides: such as WSe₂ and MoSe₂, have similar structures and mechanisms of action to disulfides, but selenium atoms are more likely to participate in redox reactions and release selenium species, which may cause DNA breaks and gene mutations [45,46].

Black phosphorus: black phosphorus is easily degraded in biological environments, can oxidize lipids, induce excessive production of reactive oxygen species (ROS) and cause cell death, and has high cytotoxicity [48,66]. Therefore, surface modification is needed to improve its stability. At present, there are still limited studies on its effects on DNA, proteins, and other biological structures.

MXenes: such as Ti₃C₂T_X (where T_X denotes surface terminations, e.g., -OH, -O, and -F), although transition metals such as Ti, Ta, and Nb are generally considered less harmful, studies have shown that MXene nanosheets may negatively affect early embryonic development and angiogenesis [49], and high concentrations of Ti₃C₂ can induce autophagy dysfunction, resulting in cytotoxicity [50].

Hexagonal Boron Nitride (h-BN): most studies show that h-BN has good biocompatibility similar to graphene, but boron nitride is more difficult to undergo redox reactions than graphene. It may also lead to the generation of ROS at high doses, and then induce modifications to DNA structure and proteins in cells [51].

Based on the literature, we have categorized the relative toxicities of several representative 2D materials into three levels (Low, Medium, High) for comparative purposes, as summarized in Table 1. Generally speaking, 2D materials with small size and good dispersion are more likely to exhibit relatively low cytotoxicity, which is more conducive to achieving safe and effective detection. 2D materials mostly affect cell activity by leading to elevated ROS levels and destroying the structure of membranes, proteins and DNA [86]. In the process of wearable or implantable 2D material biosensor experiments, the toxicological properties of 2D materials should be fully considered in the design stage, and the cytotoxicity should be reduced by surface functionalization [87,88].

To move beyond descriptive statements, we highlight selected quantitative findings from the literature. For graphene oxide (GO), exposure at 50 μ g/mL for 24 h in human embryonic kidney (HEK293) cells increased intracellular ROS levels by approximately 3-fold compared to controls, with a concurrent decrease in cell viability to ~65% [37]. *In vivo*, intratracheal instillation of graphene nanoplatelets in mice at 10 μ g per mouse induced ROS-mediated DNA strand breaks in lung tissue within 24 h, detectable by comet assay [39]. For MoS₂ nanosheets (0.5–5 μ g/mL, 24 h), BEAS-2B epithelial cells showed a dose-dependent increase in lipid peroxidation (malondialdehyde up to 2.5-fold at 5 μ g/mL) and a 40% reduction in cell viability at the highest concentration, with ferroptosis as the primary mechanism [43]. Black phosphorus (BP) nanosheets at 20 μ g/mL induced cell death in over 80% of lung epithelial cells within 48 h, accompanied by a 5-fold increase in ROS and significant depletion of glu-

tathione [66]. Importantly, most quantitative cytotoxicity data originate from *in vitro* assays using isolated cell lines (e.g., HEK293, BEAS-2B, THP-1) with exposure times of 24–72 h. These conditions differ markedly from *in vivo* scenarios, where 2D materials may persist in tissues for weeks, undergo biodegradation, and interact with complex immune and extracellular matrix components. Direct extrapolation from *in vitro* to *in vivo* toxicity is therefore not straightforward, and chronic, low-dose exposure studies in animal models remain scarce.

As noted above, most *in vitro* assays use acute, high-dose exposures that do not fully represent chronic *in vivo* conditions. Although these conventional assays have reported relatively low cytotoxicity for many 2D materials, future development directions of 2D material FET biosensors include long-term *in vivo* sensing and implantable applications, which require interdisciplinary re-evaluation of their biosafety under realistic exposure scenarios. At present, cytotoxicity assessments of most 2D materials mainly rely on short-term *in vitro* assays, such as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), lactate dehydrogenase (LDH) release, cell viability, membrane integrity, and ROS measurements, which are typically conducted within 24–48 h using isolated cell lines. However, implantable or long-term biosensors may remain in complex biological environments for weeks or even months, continuously interacting with proteins, immune systems, extracellular matrices, and dynamic biofluids [45,49]. Under such conditions, long-term material degradation, chronic ROS accumulation, persistent inflammatory responses, and nanoparticle retention in organs such as the liver, spleen, and lungs may become more critical than the acute cytotoxicity observed in short-term experiments [45,85]. Some recent studies have begun to focus on the long-term *in vivo* behaviors of graphene and other 2D materials, while several reviews have pointed out that long-term, repeated-dose, and chronic-exposure toxicological studies are still insufficient, particularly under realistic *in vivo* conditions.

In addition, substantial differences in experimental conditions, including cell type, exposure concentration, incubation duration, dispersion methods, and material preparation routes, also contribute to inconsistencies among reported studies. Many current cytotoxicity studies mainly focus on single evaluation indicators, such as cell viability, ROS generation, or membrane integrity, while systematic evaluations involving long-term biological behavior, immune response, biodistribution, and chronic toxicity remain limited; additionally, differences in cell types, material preparation methods, exposure conditions, and treatment protocols among studies make direct horizontal comparison difficult, and current studies mainly clarify possible toxicity mechanisms rather than providing standardized overall biosafety evaluation. Existing *in vitro* assays are often unable to fully reproduce the complexity of real biolog-

ical environments, including protein corona formation, immune activation, blood circulation, and long-term oxidative stress [33,36,49]. Therefore, when evaluating 2D materials for wearable or implantable long-term biosensing applications, conventional short-term cytotoxicity assays alone may be insufficient. Comprehensive interdisciplinary evaluation involving materials science, biology, medicine, immunology, and toxicology is still required to investigate the long-term stability, biodistribution, and chronic toxicity of 2D materials under dynamic biological environments. Due to the long experimental duration, high cost, complex variables, and lack of standardized protocols, relevant long-term *in vivo* studies remain relatively limited.

2.2 Immune Response

In the development of implantable devices and long-term *in vivo* sensing applications, it is necessary to consider the immune response induced by 2D material FET biosensors and the potential interaction with the host immune system. This may not only harm the organism but also damage the sensor structure, affecting detection performance. At present, 2D material FET biosensors often employ surface modification using ethylene glycol (EG)-based materials and related derivatives, such as polyethylene glycol (PEG) [66], ethylene glycol combined with zwitterionic materials (EG+ZW) [89]. These materials can form highly hydrophilic structures on the sensor surface, effectively blocking the adsorption of non-specific proteins and reducing nonspecific protein adsorption. This surface functionalization strategy can reduce immune recognition of the sensor and alleviate immune responses. Researchers have selected materials with excellent anti-protein adsorption properties by constructing a combined structure of polyacrylamide-based (PAAM) copolymer hydrogel, which can effectively prevent the non-specific attachment of proteins in serum and platelet-rich plasma, thereby alleviating the activation and rejection of the sensor by the immune system [90]. The quantitative counts of platelets on PEG and the hydrogel are presented in Fig. 1 (Ref. [90]). Mechanical irritation-induced immune responses were effectively reduced by constructing graphene FET arrays on polyimide (PI). Due to the good flexibility of PI, the sensor can maintain good stability even after repeated bending [91]. Beyond platelet adhesion, a more complete assessment of immune response requires measuring cytokine secretion and immune cell activation. For graphene-based materials, studies in murine macrophage cell lines (RAW 264.7) have shown that exposure to pristine graphene (10 $\mu\text{g/mL}$, 24 h) increases TNF- α and IL-6 secretion by 2- to 3-fold relative to controls, indicating an inflammatory response [92]. However, surface PEGylation (2 kDa PEG, 0.5 wt% loading) reduced cytokine levels to near-baseline values, demonstrating the mitigating effect of antifouling layers. *In vivo*, subcutaneous implantation of graphene FET arrays on polyimide substrates in rats resulted in a localized fibrotic capsule

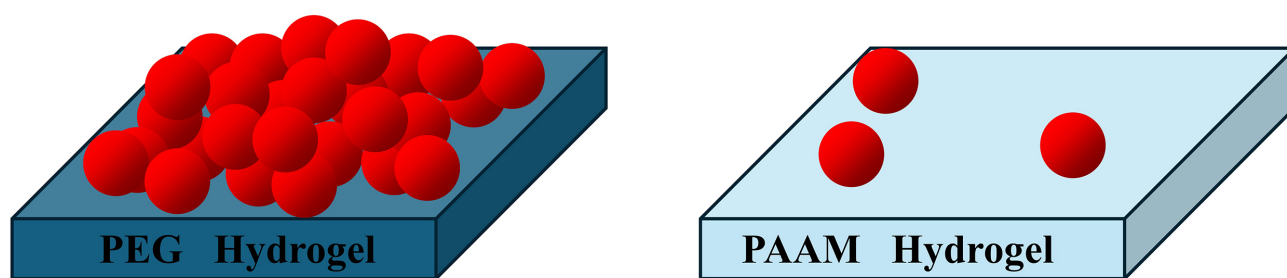


Fig. 1. Schematic diagram of platelet adhesion on the hydrogel surface based on PEG and PAAM [90]. Compared with PEG matrix, PAAM based hydrogel shows significantly reduced platelet adhesion, indicating that it has excellent anti adhesion performance. PAAM, polyacrylamide-based.

thickness of $\sim 38\ \mu\text{m}$ after 4 weeks, significantly thinner than that observed for uncoated silicon devices ($\sim 76\ \mu\text{m}$), suggesting that flexible, functionalized substrates provoke a milder foreign body response [93]. These quantitative data underscore that the immune response is highly dependent on surface chemistry, material dimensions, and implantation context. Most current studies, however, are limited to short-term (days to weeks) evaluations, and long-term (months) immune effects in realistic physiological environments remain insufficiently characterized. Taken together, these quantitative findings demonstrate that surface functionalization and material optimization can significantly reduce immune responses and improve the stability of 2D material FET biosensors. However, most current studies are still limited to short-term biological evaluations (days to weeks), and the long-term immune effects under realistic physiological conditions remain insufficiently understood.

2.3 Long-Term Stability and Chronic Biosafety of 2D Materials

Although many studies discussed in Section 1 mainly focus on short-term cytotoxicity of 2D materials under conventional *in vitro* conditions, we believe that long-term stability is one of the most critical factors affecting their chronic biosafety in practical *in vivo* applications. The excellent short-term biocompatibility observed in laboratory conditions does not necessarily guarantee long-term biosafety, because degradation, oxidation, hydrolysis, and long-term bio-interface interactions may gradually alter the physicochemical properties and biological behaviors of 2D materials under dynamic physiological environments. Importantly, the stability of 2D materials not only affects the sensing performance and operational lifetime of biosensors, but may also influence their long-term toxicity. Whether 2D material-based FET biosensors can maintain their initially observed “low toxicity” under long-term biological exposure conditions is closely related to their long-term stability. Graphene and its derivatives and transition metal disulfides have excellent chemical inertness and thermal stability, but they easily adsorb pollutants such as water and oxygen in the air, resulting in degradation of electronic

properties [94]. The research shows that MoS_2 will crack along the sawtooth direction in the long-term exposure to oxygen environment, especially under the condition of wet oxygen [95]. In addition, monolayer graphene exhibits increased susceptibility to oxidation due to its large surface area and abundant edge active sites, resulting in the decline of its electronic properties [96]. In contrast, the stability of BP in the environment is poorer, and it readily undergoes hydrolysis and oxidation reactions in the air, resulting in rapid degradation of the structure and properties of the material [97]. Although BP exhibits good carrier mobility and tunable bandgap for biosensing applications, its poor environmental stability may significantly limit its practical applicability in long-term implantable or *in vivo* biosensors. The stability of 2D materials is a critical factor for biosensor performance and can be enhanced through covalent functionalization (CF) [98], polymer encapsulation [99], doping [100] and other methods.

The majority of cytotoxicity studies rely on *in vitro* assays (e.g., MTT, LDH, ROS measurement) using immortalized cell lines exposed to high, acute doses of 2D materials for 24–72 h. While these assays are useful for initial safety screening and mechanistic elucidation (e.g., identifying ROS pathways), they do not faithfully replicate the conditions of chronic *in vivo* exposure relevant to implantable or long-term wearable biosensors. In the body, 2D materials may be gradually released from the sensor surface due to degradation, form a protein corona that alters their biological identity, be phagocytosed by macrophages, and persist in tissues for extended periods [101]. Furthermore, *in vivo* concentrations are typically orders of magnitude lower than those used in *in vitro* tests, but the exposure duration is much longer (weeks to months) [102]. For example, *in vitro* studies often use GO at 10–100 $\mu\text{g/mL}$ for 24 h, whereas *in vivo* leaching from an implant might be in the ng/mL range over months. Direct extrapolation of *in vitro* EC_{50} values to *in vivo* safety thresholds is therefore inappropriate. Systematic *in vivo* studies using low-dose, long-term exposure protocols (e.g., 28-day or 90-day repeated-dose studies) with comprehensive histopathology, biodistribution, and clearance analysis are urgently needed. To date, only a handful

of such studies exist for graphene and MoS₂, and virtually none for most emerging 2D materials (e.g., MXenes, diselenides) in the context of biosensor applications.

Overall, many 2D materials exhibit relatively low cytotoxicity and good biocompatibility under short-term experimental conditions, demonstrating their great potential for biosensing applications [38,51,85]. However, achieving long-term dynamic *in vivo* sensing still faces substantial challenges. First, systematic studies regarding the chronic toxicity of 2D materials remain insufficient, particularly under realistic physiological conditions [45,85]. Second, unexpected long-term retention of 2D materials in tissues or organs may introduce additional biosafety concerns, especially in the absence of effective clearance mechanisms. Excessive accumulation of nanomaterials in the liver, spleen, and lungs may further increase the risks of chronic inflammatory responses and long-term biological effects. Importantly, although surface functionalization is commonly employed to improve the stability and biocompatibility of 2D materials, complex functionalization processes may themselves introduce new biosafety risks, including chemical residues, immune responses, and unpredictable biological behaviors [98,99]. Therefore, considerable challenges still remain before 2D material-based FET biosensors can achieve practical long-term *in vivo* applications.

Future development of 2D material FET biosensors should focus not only on sensing performance and short-term biocompatibility, but also prioritize investigations into chronic toxicity, degradation behavior, biodistribution, and safe clearance mechanisms under physiological environments [94,95,96,97]. In addition, safer, controllable, and reproducible functionalization strategies are still required to improve stability and sensing performance while minimizing long-term biosafety risks, thereby promoting the practical translation of 2D material biosensors for *in vivo* applications.

3. Covalent Functionalization

Two dimensional materials have attracted considerable attention in FET biosensors due to their high specific surface area and excellent electron mobility [19]. However, most 2D materials have poor selectivity towards biomolecules or are difficult to connect with biomolecules themselves. When directly exposed to complex detection environments, they may also face issues of poor stability and weak specificity. Therefore, 2D materials need to be modified by surface functionalization. CF can improve its chemical stability and functional diversity by introducing covalent bonds on the surface of 2D materials.

3.1 Radical-Initiated Reaction

Free radical initiation reactions use highly active free radical intermediates to form covalent bonds with the surface of 2D materials, thereby enabling functional modifi-

cation of materials. Aromatic diazonium salts can decompose under suitable conditions to produce aromatic groups and release nitrogen gas. These aromatic groups can react with SP² carbon atoms on the surface of 2D materials such as graphene and carbon nanotubes to form C-C covalent bonds, facilitating subsequent functionalization and sample detection [103]. 4-Nitrobenzene diazo tetrafluoroborate was used to selectively excite CNTs with specific chiral structures under light conditions, as shown in Fig. 2a (Ref. [104]), enabling selective functionalization of CNTs at specific positions, offering a strategy to control the optical and electronic characteristics of carbon nanomaterials [104]. Functionalization at sulfur vacancies of MoS₂ was achieved by 4-nitrobenzene diazonium tetrafluoroborate (4-NBD) at 35 °C and 125 rpm without affecting the properties of the MoS₂ material [105]. The treatment process was simple and the reaction conditions were mild. In addition to aryl diazonium salts, some azo compounds can also undergo decomposition reactions under light or heating conditions, releasing nitrogen gas and producing highly reactive free radicals. This property was utilized to functionalize reduced graphene oxide (RGO): two covalently bonded azobenzene (AZO) molecules fixed onto RGO can change its surface properties by altering the state of AZO molecules under light irradiation [106]. Although the original intention of this study was to develop efficient solar thermal storage materials, this approach may also be applicable to biosensors. This functionalization method not only endows the material with good thermodynamic stability, enabling long-term detection in warm environments, but also leverages its unique energy storage properties to provide the possibility of developing self-powered biosensors. In the CF of 2D materials, peroxides are often used as initiators of free radical reactions. Benzoyl peroxide (BPO) molecules absorbed by graphene were decomposed into free radicals at 80 °C, as shown in Fig. 2b (Ref. [107]), to achieve large-scale functional modification of graphene [107]. This method is relatively simple and may be suitable for large-scale functionalization.

In the functionalization process of 2D materials, common active sites include sp² hybridized carbon atoms and defect sites such as sulfur vacancies. Attributable to the high density of electrons, it is often difficult to directly bind target analytes or probes to these sites. However, by introducing free radicals to achieve functionalization, the surface of 2D materials has the possibility of connecting more types of biomolecules, and through subsequent functionalization design, it can ultimately bind with the target detection substance. Most current radical-induced covalent functionalization strategies are still mainly based on large-area surface modification, while single-molecule detection often requires more localized and controllable functionalization. Achieving precise interface regulation while maintaining functionalization stability remains a challenge for future studies [104,105].

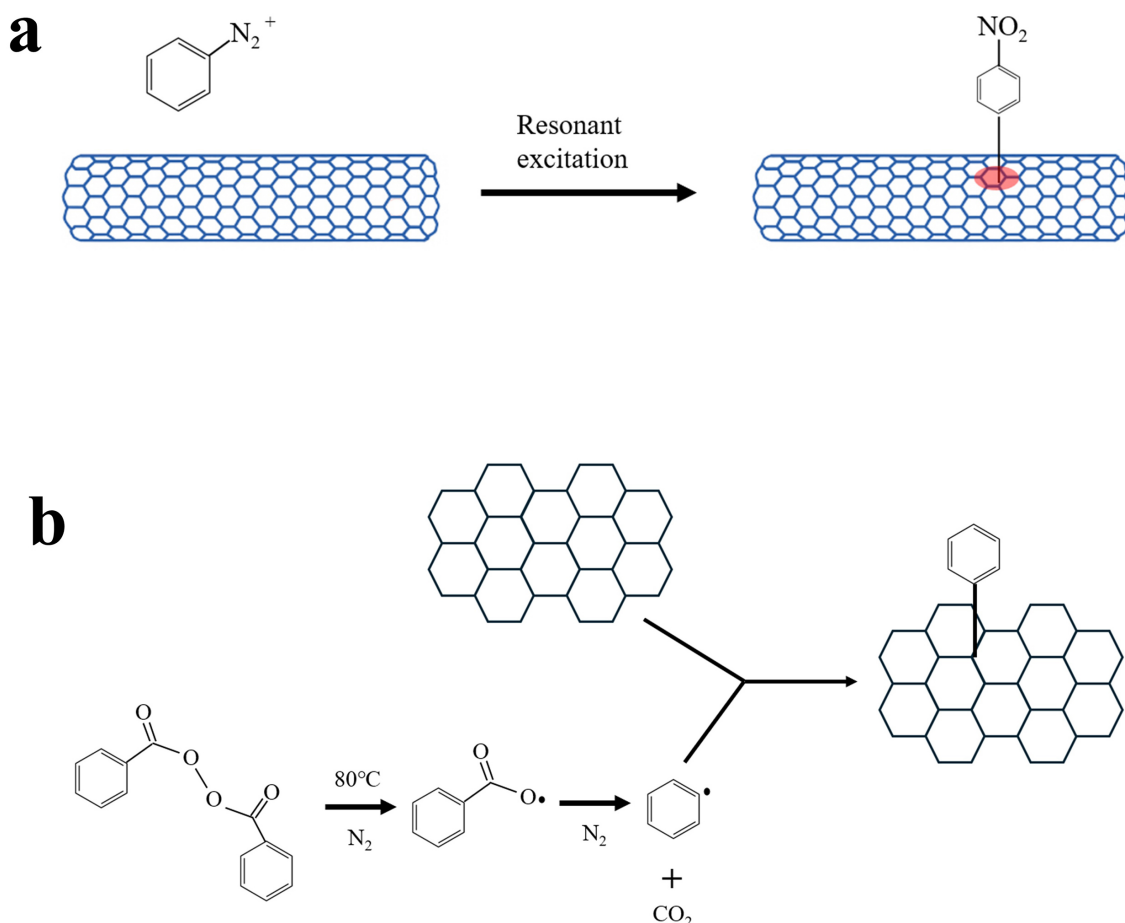


Fig. 2. Representative radical-initiated covalent functionalization mechanisms. (a) Proposed functionalization mechanism with aryl diazonium [104]. (b) Direct radical mechanism for BPO functionalization [107]. Light selectively excites carbon nanotubes with specific chirality, enabling site-specific covalent bonding of aromatic groups. The BPO molecules adsorbed on graphene decompose and convert into free radicals at 80°C , achieving CF. BPO, benzoyl peroxide; CF, covalent functionalization.

3.2 Cycloaddition Reactions

In the preparation process of 2D materials, cycloaddition reactions can also be used to introduce different functional groups. These reactions usually occur under mild conditions and generally do not damage the architecture and electrical properties of the 2D material itself. Tetracyanoethylene oxide (TCNEO) was covalently attached to the graphene surface via the Diels–Alder reaction [108]. Next, solid-phase peptide synthesis (SPPS) technology was employed to synthesize and connect peptide chains containing His and HA tags on TCNEO modified graphene, introducing specific biomolecular recognition sites. This strategy can be used to construct high-sensitivity biosensors and neural interface devices.

3.3 Nucleophilic Addition Reactions

Nucleophilic addition reaction is a common and efficient functionalization method for 2D material surfaces. The mechanism involves the reaction between nucleophilic reagents and electronic defect sites on the surface of a 2D

system, which breaks the π bond to generate new σ bonds and achieve stable covalent bonding [109]. This type of reaction includes direct addition, conjugated addition, nucleophilic ring opening reaction, etc. Most nucleophilic reactions can proceed at room temperature or slightly higher temperatures, without the need for strong catalysts or strong acid-base environments, and making them suitable for constructing complex functional structures [110,111]. The carboxymethyl group ($-\text{CH}_2\text{COOH}$) was introduced on exfoliated 1T-MoS₂ via a nucleophilic reaction to achieve functionalization, as shown in Fig. 3 (Ref. [112]). This method can effectively reduce charge transfer resistance, which may help improve sensing performance [112]. The electrophilic reaction between maleimide molecules and sulfur atoms on the surface of MoS₂/WS₂ through Michael addition was utilized to achieve functionalization [113]. This method does not require high temperatures or strong catalysts, and can form a stable organic modification layer on the surface of the 2D material while preserving its lattice integrity. They subsequently confirmed through scanning tunneling microscopy (STM) and atomic force mi-

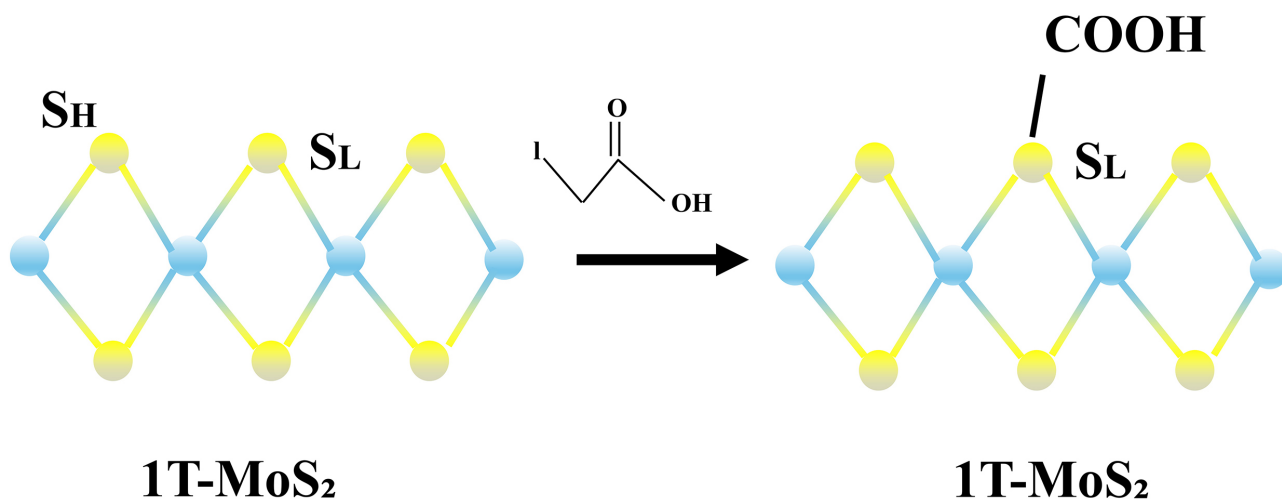


Fig. 3. Functionalization of 1T-MoS₂ via affinity reaction for -CH₂COOH grafting [112]. Using nucleophilic reaction, introduce -CH₂COOH into the peeled metal phase 1T-MoS₂ surface.

croscopy (AFM) observations that maleimide molecules can covalently bond with MoS₂, while the edges or defect regions of MoS₂ exhibit physical adsorption behavior, indicating that the reaction has regional selectivity. A covalent modification strategy was systematically investigated, in which cysteamine (CA) was grafted onto the surfaces of GO and rGO through a base-catalyzed thiol–ene Michael addition (TEMA) reaction [114]. They demonstrated three different functionalization pathways for comparison: free radical functionalization, nucleophilic functionalization of graphene, and nucleophilic functionalization of oxidized graphene. The results showed that after heating, there was a reaction between thiol and α , β -unsaturated acids on GO, suggesting a possible route for GO functionalization through thiol ene reaction. Epoxy groups on the GO surface were functionalized with Na₂S as a nucleophile, and subsequently formed a four membered ring (fMR) by introducing oxygen atoms [115]. The coordination between cadmium (Cd) and sulfur (S) atoms exerts additional stress on the quaternary ring containing heteroatoms, inducing the C-C bond cleavage of the quaternary ring on the surface of rGO. Although this study mainly focuses on photocatalytic hydrogen production and optoelectronic applications, its functionalization strategy may also be useful for surface modification and signal transduction of 2D material based FET biosensors, providing new design ideas for constructing high-sensitivity biosensors and for detecting Cd and S related species.

3.4 Silanization Reaction

Silanization reaction is a commonly used functionalization method, in which organic silane molecules form Si-O-Si covalent bonds with the surface of the oxide material in 2D FET biosensors. Surface self-assembled monolayers can be used to introduce active functional groups and immobilize biomolecular probes. A biosensor

was made based on a suspended MoS₂ atomic layer and a nanogap electrode. The self-assembled amino functional group layer was formed on the surface of HfO₂ by (3-aminopropyl)triethoxysilane (APTES) and reacted with glutaraldehyde to achieve functionalization [116]. The silane layer can provide a highly compatible bridging structure, ensuring that antibodies can be efficiently and stably fixed on the sensor surface. This FET biosensor can produce significant current response changes toward *Escherichia coli* at a concentration of 10 colony-forming units (CFU)/mL, demonstrating high sensitivity and stability. A 30 nm-thick atomic layer deposition (ALD) layer of Al₂O₃ was deposited on the surface of MoS₂ grown by chemical vapor deposition (CVD). The surface of Al₂O₃ naturally contains -OH groups, which can react with APTES and introduce -NH₂ [117]. Afterward, glutaraldehyde was used for crosslinking, and finally the biomolecule immunoglobulin G was covalently immobilized, which can specifically bind to the target biomolecule and alter the electrical properties of the sensor. Xiao Li's research team has developed a fluorescent biosensor using PEG functionalized MoS₂ nanosheets for detecting the activity of intracellular caspase-3 (Fig. 4a) [118]. They first introduced a layer of Polydopamine on the surface of MoS₂, followed by PEG to form a composite structure, and then attached the peptide to the composite structure to detect the activity of caspase-3 through fluorescence reaction. The LOD was further reduced to 0.33 ng/mL. The affinity functionalization method demonstrated in this study can enable peptides to better bind to the surface of materials, and the binding affinity was 3.08 times higher than that of traditional thiol metal coordination methods. This functionalization method can also provide useful strategies for the development of 2D material FET biosensors. When functionalizing the surface of 2D materials, there are various types of silane reagents, and their different

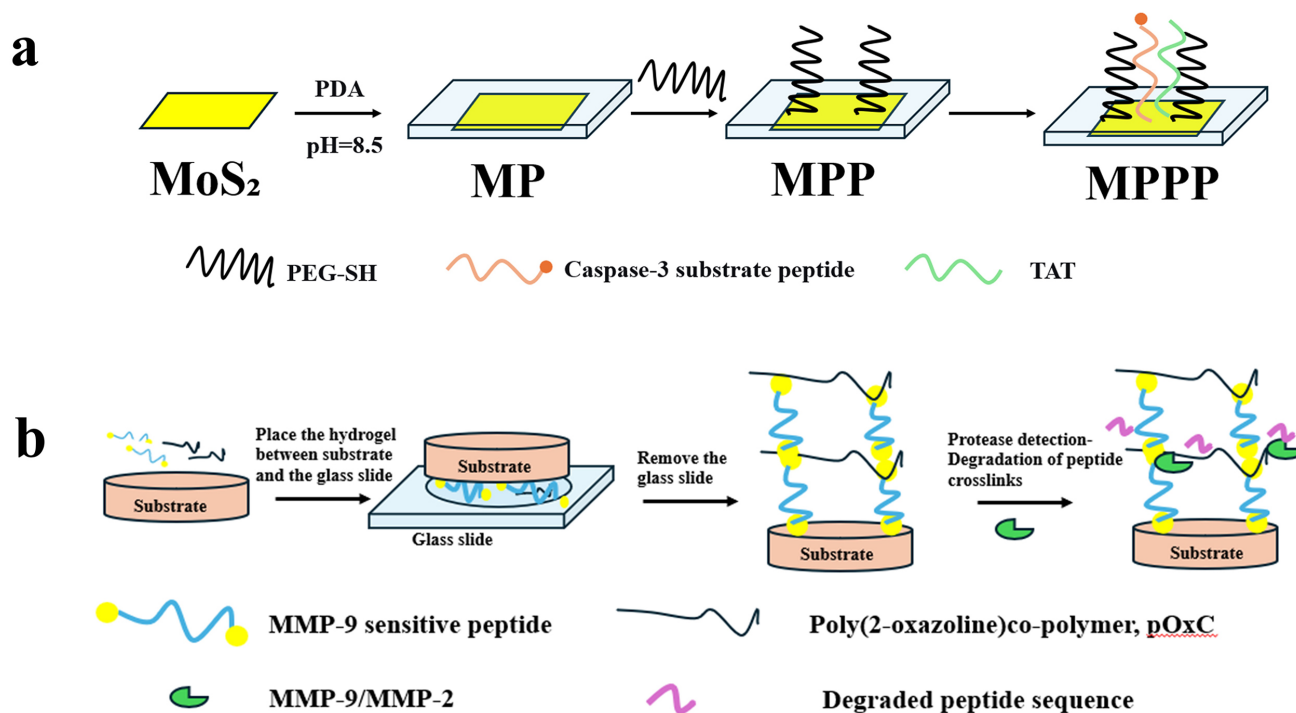


Fig. 4. Representative polymer-based functionalization and biosensing strategies. (a) Preparation of polydopamine-coated MoS₂. Based on the experimental scheme reported by Li et al. [118]. (b) Sensor fabrication and detection of MMP-9 [121]. Under alkaline conditions, dopamine polymerizes on the surface of MoS₂ to form a PDA coating layer (MP). Later, thiol PEG was introduced through Michael addition to obtain MPP. Subsequently, the Caspase-3 substrate peptide was covalently attached to the surface of MPP, and the probe was inserted to ultimately form MPPP. The hydrogel solution containing specific polypeptide cross-linking agent is placed between the substrate and the glass slide, and then the glass slide is removed to form a flat hydrogel film on the substrate. When the target protease exists, it will specifically recognize and cut the polypeptide of the hydrogel, resulting in electrical structure changes, which can be detected as electrical signal changes.

functional groups at the end can be used to introduce various intermediate functionalized molecules. APTES and N-(2-aminoethyl)-3-aminopropyltrimethoxysilane (AEAPS) can provide -NH₂, which can then react with crosslinking agents such as glutaraldehyde or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC)/N-hydroxysuccinimide (NHS) for subsequent biomolecule immobilization [116,119]. MP TES can introduce -SH groups, which can form stable metal sulfur covalent bonds with metal ions, thereby facilitating metal-ion detection in biological environments [120].

3.5 Polymer Functionalization

Polymer functionalization is mostly achieved through CF onto the surface of 2D materials, with a small portion being able to connect through non-covalent interactions such as physical adsorption. There are various types of polymers, and they generally have good biocompatibility. Sensor performance can be optimized by expanding multiple functional groups and controlling the length and structure of polymer chains. PEG has good hydrophilicity, low toxicity, and good biocompatibility, making it widely used for functionalizing 2D materials [31]. Norlaily Ahmad's research

team has developed a new biosensor material based on peptide crosslinked poly (2-oxazoline) (pOx) hydrogel (Fig. 4b, Ref. [121]), which is used for single use protease detection. The LOD of metalloproteinase-9 (MMP-9) is 10 nM [121]. Polysarcosine has excellent biocompatibility and can maintain good stability *in vivo*, making it less likely to cause biological immune reactions. Currently, it is being used in the fields of drug delivery, mRNA delivery, antibody drug conjugates (ADCs), and has the ability to effectively improve the biocompatibility and detection sensitivity of 2D materials such as graphene and molybdenum disulfide [122,123]. Thanks to the high designability of polymers in terms of structure and function, significant progress has been made in their application in multimolecule detection in recent years. A polymer was synthesized for functionalizing the gate of FET using molecular imprinting technology. Poly (3,4-ethylenedioxythiophene) - poly (styrene sulfonate) functionalized multi-walled carbon nanotubes were used to simultaneously detect adrenaline (AD) and uric acid (UA), significantly improving the sensing selectivity and sensing sensitivity [124]. The research results show that the LODs of the sensor for AD and UA are 1 pM. It provides linear ranges of 0.5 pM to 10 μM for AD, while the

range of UA extends from 1 pM to 1 mM, respectively, with a response time of 2 seconds. With the continuous development of new functional polymers and the continuous optimization of modification processes, polymer functionalization technology, with its excellent scalability, may further promote the development of high-sensitivity and multifunctional integrated biosensors, providing assistance for the continuous development of multimolecule detection, precision medicine, and instant diagnosis.

Although most 2D materials cannot directly target biomolecules on their surfaces, by modifying specific reaction sites (such as defects or sulfur vacancies on sp^2 carbon structures) and combining CF strategies such as free radical reactions, cycloaddition reactions, nucleophilic addition, silanization, and polymer functionalization, 2D materials can quickly form stable chemical connections with biomolecules, helping improve detection efficiency and broaden sensing applications for 2D FET biosensors [125].

3.6 Critical Appraisal of CF Strategies: A Mechanistic Perspective

While the above sections detail various CF chemistries (radical, cycloaddition, nucleophilic, silanization, etc.), a critical comparison from a biosensing-device perspective is essential. CF methods create permanent, stable linkages, which fundamentally influence device performance across several key parameters.

3.6.1 Signal Stability and Transduction Efficiency

The strong, irreversible bonds in CF ensure minimal signal drift over time, a critical advantage for long-term or continuous monitoring [126]. However, this stability comes with potential drawbacks. Many CF reactions (e.g., radical-initiated) can introduce substantial sp^3 defects into the 2D material lattice, which, while creating reactive sites, also act as charge scattering centers [127]. This can significantly reduce carrier mobility, directly attenuating the FET's transconductance and thus the signal-to-noise ratio. Furthermore, the often-rigid linkers in CF (e.g., amide bonds from EDC/NHS) can place the bioreceptor probe far from the channel surface, potentially pushing the target binding event beyond the Debye length and nullifying the charge-sensing advantage [128].

3.6.2 Alleviation of the Debye Screening Effect

CF allows for precise molecular design. By using short-chain crosslinkers (e.g., a short silane or a minimal peptide linker), the biorecognition layer can be kept exceptionally thin [129]. This is the most direct CF strategy to mitigate Debye screening, enabling sensitive detection in physiological ionic-strength samples. For example, the direct covalent attachment of aptamers via short linkers (Sections 3.4, 3.5) is superior to methods employing long polymer spacers in this regard.

3.6.3 Reproducibility and Scalability for Clinical Translation

This is a major hurdle for CF. The multi-step reactions, the need for precise control over reaction conditions (temperature, time, concentration), and the sensitivity to surface defect density on the 2D material lead to significant batch-to-batch and device-to-device variation. Silanization (Section 3.4), while widely used, is notoriously difficult to control, often resulting in non-uniform multilayers rather than a desired monolayer, leading to irreproducible sensor baselines and sensitivity [130]. For clinical application, where strict quality control is mandatory, the inherent variability of many CF processes poses a formidable challenge. While polymer functionalization (Section 3.5) offers scalability for certain applications (e.g., glucose sensors), achieving uniform, controlled covalent attachment of specific bioreceptors on a wafer-scale remains an open problem. Moreover, wafer-scale covalent functionalization must also be compatible with subsequent packaging and interconnection steps, which impose additional constraints on reagent handling, temperature budgets, and surface cleanliness.

3.6.4 Trade-Offs in Practical Applicability

The strength of CF—its irreversibility—is also a weakness. It makes sensor regeneration and reuse extremely difficult. A covalently fouled sensor surface is generally discarded, increasing the cost-per-test. Moreover, the harsh chemical conditions used in some CF reactions (e.g., radical initiators, strong nucleophiles) can be incompatible with the delicate structure of some bioreceptors (e.g., antibodies), necessitating a post-functionalization conjugation strategy that adds complexity [131].

In summary, CF is the method of choice when uncompromising long-term stability, minimal signal drift, and optimal Debye-length control are paramount. However, this comes at the cost of increased process complexity, poorer device-to-device reproducibility, limited reusability, and potential damage to the 2D material's electronic properties.

4. Non-Covalent Functionalization (NCF)

NCF is different from CF in terms of chemical bonding. Generally, functionalization molecules are attached to the surface of 2D materials through weak interactions, which makes NCF a very important functionalization method. NCF can endow materials with new biological properties while maintaining their lattice structure integrity [132]. In some cases, it is necessary to introduce specific biomolecules through NCF before CF.

4.1 π - π Stacking

π - π stacking is a commonly used strategy for NCF of 2D material surfaces, mainly relying on defect sites on the surface of the 2D material, such as sp^2 sites. This mechanism relies on weak interactions between aromatic ring systems and van der Waals forces to achieve the binding of

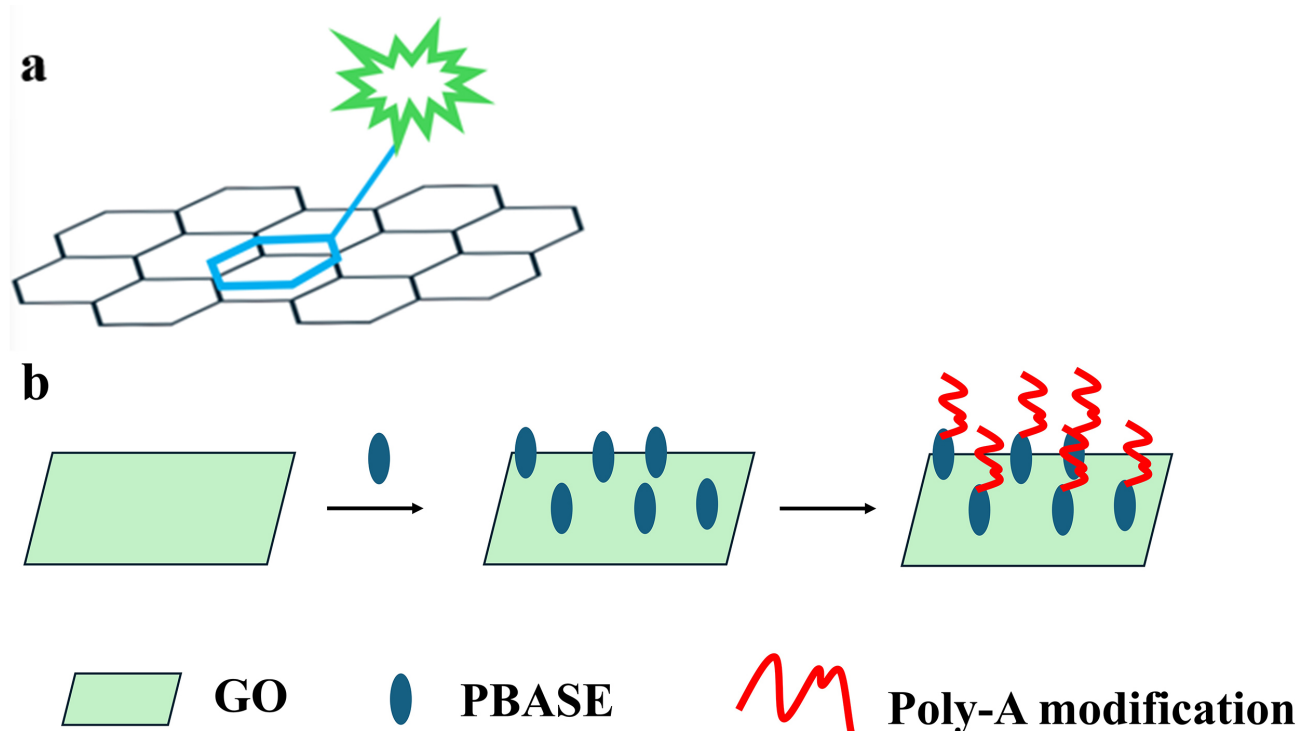


Fig. 5. Representative π - π stacking-based functionalization strategies for graphene biosensors. (a) Interaction of pyrene with graphene via π - π stacking and shared delocalized electrons [134]. (b) Functionalization of graphene surface with PBASE. Based on the experimental scheme reported by Kikuchi et al. [136]. PBASE can serve as a bridge connecting GO and poly-A modification.

functional molecules to the surface of 2D materials, without damaging the original lattice structure of the 2D materials. However, this interaction is relatively weak and may be difficult to maintain for a long time in high salt environments [133]. At the same time, it is important to note that excessive deposition on the surface of the 2D materials should be avoided, which could weaken the detection signal [15]. A pyridine lysine-based supporter construct (PLB) was functionalized using SPPS [134]. The principle was to functionalize graphene through π - π stacking (Fig. 5a, Ref. [134]), and evaluate functionalization through AFM, Raman spectroscopy, and combined with real-time electrical measurements to optimize the concentration of PLB, with an optimized concentration of approximately 1 nM. Real time electrical testing showed that upon addition of the target protein streptavidin protein solution, the FET channel current saturated within about 30 seconds, indicating that the sensor can detect streptavidin within a short time frame, while other proteins such as bovine serum albumin (BSA) did not show significant reaction, indicating to some extent its sensitivity and selectivity. Nanoscale graphene gaps were generated through dash line lithography, and a DNAzyme capable of cleaving the substrate chain under the action of copper ions was selected [135]. After mixing DNAzyme with the substrate chain, the two nanoscale gaps can be connected by π - π stacking and covalent binding of amino carboxyl groups to generate current. When cop-

per ions are added, the substrate chain breaks and the electrical signal disappears, enabling fM level detection of copper ions with good selectivity. Kantaro Kikuchi utilized the π - π interactions of pyrene groups in 1-pyrenebutanoic acid N-hydroxysuccinimide ester (PBASE) to non-covalently connect to graphene, and then used NHS groups to form amide bonds with RNA's primary amino groups to achieve covalent connection of the probe (Fig. 5b) [136]. This indicates that PBASE can be stably fixed on graphene channels through π - π stacking, while ensuring that the electrical performance of graphene does not change. Currently, PBASE is widely used in the development of 2D FET biosensors and is a common functional material. π - π stacking is a gentle and effective physical functionalization method that can connect functionalized molecules to 2D material surfaces without damaging the lattice structure, thereby achieving high-sensitivity detection of biomolecules.

4.2 Electrostatic Adsorption

Electrostatic adsorption is a functional method that utilizes the electrostatic attractions and repulsions between charged molecules and 2D material surfaces with opposite charges. An electrochemical biosensor based on GO has been developed for rapid and direct detection of *Escherichia coli* (*E. coli*) [137]. The sensor utilizes thermal embedding technology to prepare electrostatically functionalized graphene oxide electrodes on flexible substrates,

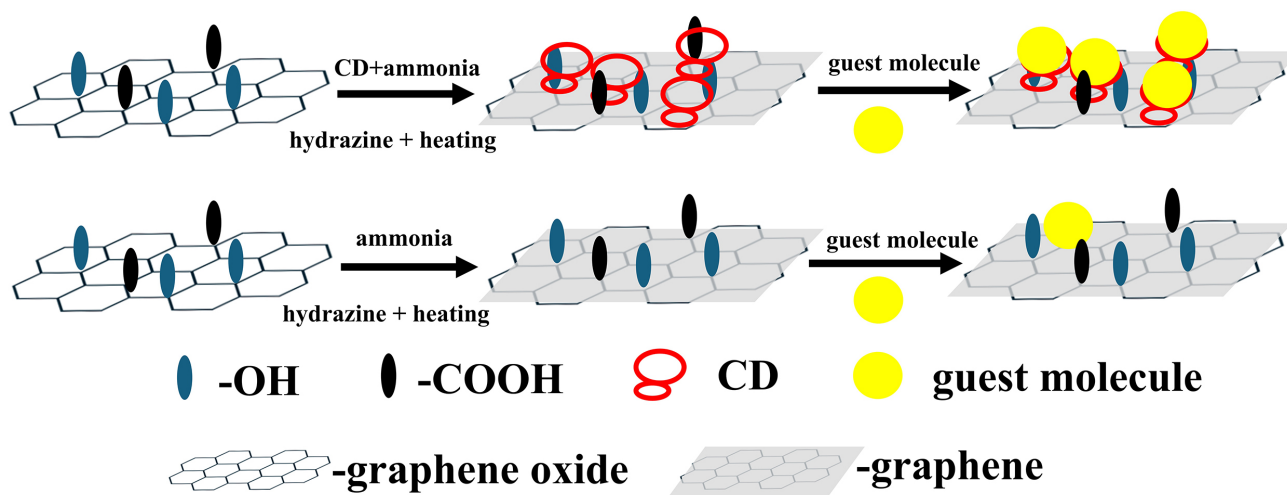


Fig. 6. The influence of CD-GN hybridization and non hybridization on host guest recognition [139]. CD-GN hybridization can reduce the π - π stacking effect, allowing GN ions to maintain dispersion and high activity, and subsequently better introduce guest molecules to improve sensor detection performance. CD, cyclodextrin; GN, graphene nanosheet.

generating positively charged rGO that can attract negatively charged bacterial cells for adsorption. At pH 7.5 and 37 °C, the optimal response range of the sensor to *Escherichia coli* is 10^{-1} to 10^{-5} CFU/mL, with a minimum LOD of 100 CFU/mL. Compared with traditional bacterial measurement methods such as agar plate culture and UV visible spectrophotometry, the correlation coefficient is 0.92, indicating good accuracy and reliability. Because of its ease of use and the absence of complex processing procedures, this sensor can be effectively applied for rapid screening and pathogen detection in food and natural water samples. NaBH_4 was used to treat liquid-phase exfoliated 2H-MoS₂, producing negatively charged n-2H-MoS₂ [138]. And it was demonstrated through various characterization methods that the surface structure of molybdenum disulfide treated by this strategy was not damaged, maintaining the integrity of the semiconductor phase and structure of 2H-MoS₂. Electrostatic adsorption is a straightforward and efficient NCF method widely used in the development of 2D material FET biosensors. It can not only achieve target molecule adsorption under mild conditions, but also enable sensor reuse by controlling electrostatic interactions to achieve functions similar to self-assembled monolayer films. It also provides reliable support for highly sensitive and selective sensor design.

4.3 Host-Guest Recognition

Host-guest recognition is a method for NCF of 2D materials through specific intermolecular binding. Through the coordination of cyclodextrin guest molecules and crown ether metal ions, molecules can be selectively adsorbed onto the surface of 2D materials, endowing them with high selective recognition ability. Graphene nanosheets (CD GNs) modified with β -cyclodextrin (β -CD) were first

reported to enhance the electrochemical sensing ability [139]. Through doping strategy and host guest synergistic effect, CD GNs exhibit several fold enhanced electrochemical response to various small molecule drugs and biomolecules, significantly better than unmodified graphene. The article describes the functionalization of graphene and graphene oxide, respectively, as illustrated in Fig. 6 (Ref. [139]). β -CD can also be used to non covalently bind bacteria or biomolecules and detect their concentration. Graphene/chitosan/ β -CD composites were constructed by a chemical reduction synthesis method for the detection of *Staphylococcus aureus*. Sortase A was used to catalyze the adsorption of *Staphylococcus aureus*, enhancing the selectivity and responsiveness of the sensor [140]. The LOD was 12 CFU/mL. Crown ethers are less commonly used in the functionalization of 2D materials, but in recent studies, dibenzo-24-crown-8 ether (DB24C8) was crosslinked with MIL-53-NH₂MOF to construct a composite material, MIL-53-NH₂-dibenzo-24-crown-8-ether nanocomposite (MOFCE24) [141]. The composite material was modified on the surface of a carbon based working electrode by drop casting method to prepare a stripping voltammetry sensor. The detection performance of the sensor is optimal in the concentration range of lead ions from 13.75 to 217.83 ppb, with a LOD of 3.18 ppb and a limit of quantification (LOQ) of 9.62 ppb. This study provides experimental evidence for introducing the host guest recognition mechanism of crown ethers into 2D material sensors, promoting the development of high-sensitivity detection of metal ions. The host guest mechanism exhibits high controllability and strong selectivity in the functionalization process of 2D materials, with significant functionalization advantages, especially in enhancing recognition sensitivity and signal transduction ability. In the research of some drug carriers, it can be used to change the wa-

ter solubility of the object and improve its stability *in vivo* [142,143]. However, its stability depends on the interfacial binding strength and environmental conditions, and integration with other functionalization strategies is often required to maintain sensor stability [144].

4.4 Doping and Defect Engineering

4.4.1 Doping Strategy

The doping strategy introduces heteroatoms to replace atoms in 2D materials, adjusts their band structure and carrier concentration, and improves their conductivity and catalytic activity. MoS₂ and WS₂ were doped with chlorine molecules, and it was found that chlorine molecule doping can significantly reduce the contact resistance and improve the performance of FETs [145]. The contact resistance of WS₂ and MoS₂ was reduced to 0.7 kΩ·μm and 0.5 kΩ·μm, respectively. A heterostructure of nitrogen-doped ReS₂ and In₂O₃ quantum dots was constructed, and nitrogen doping was found to increase the carrier mobility of ReS₂, reduce contact resistance, and improve sensor performance [146].

4.4.2 Defect Engineering

Defect engineering utilizes the defect types in the structure of 2D materials, adjusts their electronic structure and surface activity, enhances their adsorption performance, connects specific intermediate functional molecules, and improves the biocompatibility of 2D material sensors. Sanyal introduced Se vacancies through defect engineering and utilized the strong selective adsorption of NH₃ molecules by these vacancies [147]. The interaction between this structure and NH₃ molecules was significantly enhanced and the adsorption energy was increased from the original 0.12 eV to −0.97 eV, which can significantly improve the sensor performance. WSe₂ was treated with trifluoromethyl thianthrenium triflate (TTT) to passivate defects and increase hole density [148]. The WSe₂-CF₃-TIS₂ FET treated in this way achieved a hole mobility of approximately 147 cm²/V·s in p-channel mode, with good stability at 200 °C.

Doping and defect engineering, as two strategies for functionalizing 2D materials, can regulate the electronic properties and surface activity of 2D materials, and can be used simultaneously in constructing high-performance FET biosensors. Both can also achieve material functionalization without damaging the surface structural integrity of the material, providing an ideal approach for designing fast response and high stability 2D material FET biosensing platforms [21,149,150].

Compared with CF, NCF is mostly physical adsorption, with milder reaction conditions, lower selectivity, and relatively unstable structures. In the actual preparation process of 2D material FET biosensors, NCF is often combined with CF to ultimately achieve the fixation of the target molecule [151]. Firstly, intermediate functional molecules are introduced through non-covalent interactions to en-

hance the functionality of the material. Then, stable connections are then achieved through CF to optimize sensing sensitivity, selectivity, and response speed [31,150]. However, the thickness of the functionalization layer should be minimized, since excessive probe-channel distance can result in significant signal attenuation due to Debye screening effects. By comprehensively utilizing multiple functional methods, high-sensitivity detection of 2D material FET biosensors in complex environments can be achieved, providing the possibility for developing multi-component simultaneous detection and improving stability.

It should be noted that functionalization does not always reduce biosafety risks. Although some crosslinkers, polymers, and nanoparticle-assisted layers can improve interface stability and antifouling capability, they may also alter the intrinsic surface properties, biodistribution, and biological interactions of 2D materials, thereby introducing new biosafety concerns [45,85,122]. Besides improving sensing performance, the long-term biocompatibility and potential toxicological effects of functionalization strategies should also be carefully considered. In addition, higher functionalization stability is not always beneficial. In some cases, reversible or relatively weak non-covalent functionalization may facilitate interface regeneration and repeated functionalization, thereby improving sensor reusability [132]. Compared with permanent covalent modification, such reversible interfaces may exhibit poorer long-term stability, but can avoid permanent damage to 2D material surfaces and provide opportunities for interface renewal and repeated sensing applications. Moreover, functionalization design should not only focus on probe immobilization stability and selectivity, but also consider whether target binding can induce sufficiently strong interfacial charge perturbation and electrical response. In some cases, even if target molecules successfully bind to the recognition interface, FET devices may still fail to generate effective signals when conformational variation is limited or charge perturbation occurs beyond the Debye length. Therefore, functionalization strategies should also balance interface recognition and efficient electrical signal transduction [21].

4.5 Comparative Analysis of NCF: Advantages and Inherent Limitations

In contrast to CF, NCF strategies leverage weak interactions (π-π stacking, electrostatic adsorption, host-guest recognition), offering a distinctly different set of trade-offs for 2D material FET biosensors.

4.5.1 Superior Preservation of Channel Integrity and Charge Mobility

The most compelling advantage of NCF is its non-destructive nature. By avoiding the creation of sp³ defects, NCF preserves the perfect lattice structure and, consequently, the exceptional carrier mobility of the 2D material

[152]. This leads to higher transconductance and, theoretically, a larger potential signal change upon target binding, as demonstrated with PBASE (π - π stacking) in several studies (Section 4). From a charge transfer efficiency perspective, NCF is often superior.

4.5.2 Signal Stability and the Challenge of Desorption

This is the Achilles' heel of NCF. The very weakness of the interaction that preserves the lattice also makes the functional layer susceptible to displacement, especially under physiological flow conditions or in complex biofluids containing abundant competing molecules (e.g., albumin, lipids) [153]. This can lead to progressive loss of probe molecules (signal decay over time) and unacceptable baseline drift [154]. While advantageous for sensor reusability, this dynamic nature is detrimental for applications requiring long-term or quantitative stability.

4.5.3 Debye Screening Mitigation: An Indirect Approach

NCF does not inherently control probe orientation or distance as precisely as CF. While the planar pyrene group in PBASE lies flat on graphene, the attached NHS ester and subsequent bioreceptor can extend far from the surface [155]. More importantly, electrostatic adsorption (Section 3.2) can result in a randomly oriented, multi-layered protein film, with a thickness far exceeding the Debye length, rendering the sensor insensitive in high-ionic-strength media [134]. Thus, while NCF is excellent for preserving the transistor's intrinsic gain, it offers poor direct control over the critical parameter of sensing-layer thickness.

4.5.4 Reproducibility, Scalability, and Clinical Potential

NCF methods are generally simpler, faster, and more amenable to large-scale production. The "drop-cast and incubate" approach is far more scalable than multi-step covalent chemistry. However, the reproducibility is limited by the physical nature of the adsorption process, which is sensitive to concentration, temperature, time, and the exact surface morphology of the 2D material [156]. For clinical translation, this variability is a major concern. Nevertheless, the simplicity and low cost of NCF make it exceptionally attractive for single-use, disposable point-of-care (POC) devices where a slight variation between test strips is acceptable, and the primary need is for a rapid, qualitative, or semi-quantitative answer [157]. Nevertheless, even for disposable POC devices, concerns over batch-to-batch consistency, storage stability (shelf-life), and simple packaging without compromising the functionalized interface remain underexplored.

4.5.5 Synergistic Strategies

It is crucial to note that many successful biosensors employ a hybrid approach (e.g., π - π stacking of PBASE as an anchor, followed by covalent attachment of the probe via amide bonding). This clever design seeks to combine the

lattice-preserving, stable adsorption of NCF with the specific, oriented probe immobilization of CF.

In conclusion, the choice between CF and NCF is not about which is "better", but which is more appropriate for the application scenario. NCF excels for rapid, low-cost, single-use diagnostics where preserving 2D material mobility is key and long-term stability is not required. CF is indispensable for implantable, long-term monitoring, and quantitative assays where stability and Debye-length control are non-negotiable, albeit at the price of greater complexity and variability.

5. Application Progress of 2D Material FET Sensors

2D FET biosensors utilize 2D materials as channel materials, which feature an increased surface-to-volume ratio along with favorable electrical properties. By designing appropriate functionalization strategies, they can meet the detection needs in specific scenarios and show remarkable performance in the fields of biomolecule and metal ion detection. This type of sensor achieves high sensitivity and selective sensing of biomolecular targets including nucleic acids, proteins, saccharide, as well as heavy metal ions such as Pb^{2+} without labeling, with a short response time [31,158]. It has important application value in early medical diagnostics and rapid monitoring of disease states [159,160]. Due to the Debye screening effect, 2D material FET biosensors generally exhibit better performance for small-molecule detection, while the detection of large biomolecules such as proteins still faces significant challenges. In addition, many current studies are still mainly validated under ideal buffer conditions, while long-term sensing data in complex real biological environments remain relatively limited.

5.1 Nucleic Acid Detection

5.1.1 DNA Detection

The 2D FET biosensor offers advantages such as label-free detection, real-time monitoring, and the ability to detect DNA at trace concentrations. However, in recent years, literature trends have shown that research enthusiasm for pure DNA testing has declined, with directions gradually shifting toward multi-component detection of disease biomarkers, proteins, viruses, as well as integrated and chip-level sensing systems. Below, we organize representative DNA detection strategies according to their functionalization approaches.

Nanomaterial-mediated bridging strategies. One effective approach employs metallic or carbon nanomaterials as intermediate linkers between the 2D channel and DNA probes. Liu et al. [52] used gold nanoparticles as bridges on MoS_2 channels to detect predefined DNA fragments on chromosomes 21 or 13 (Fig. 7a, Ref. [52]), achieving an LOD below 100 aM, a method that could reduce false negatives in non-invasive prenatal testing (NIPT) [161]. Similarly, Shariati et al. [56] developed ZnO-doped

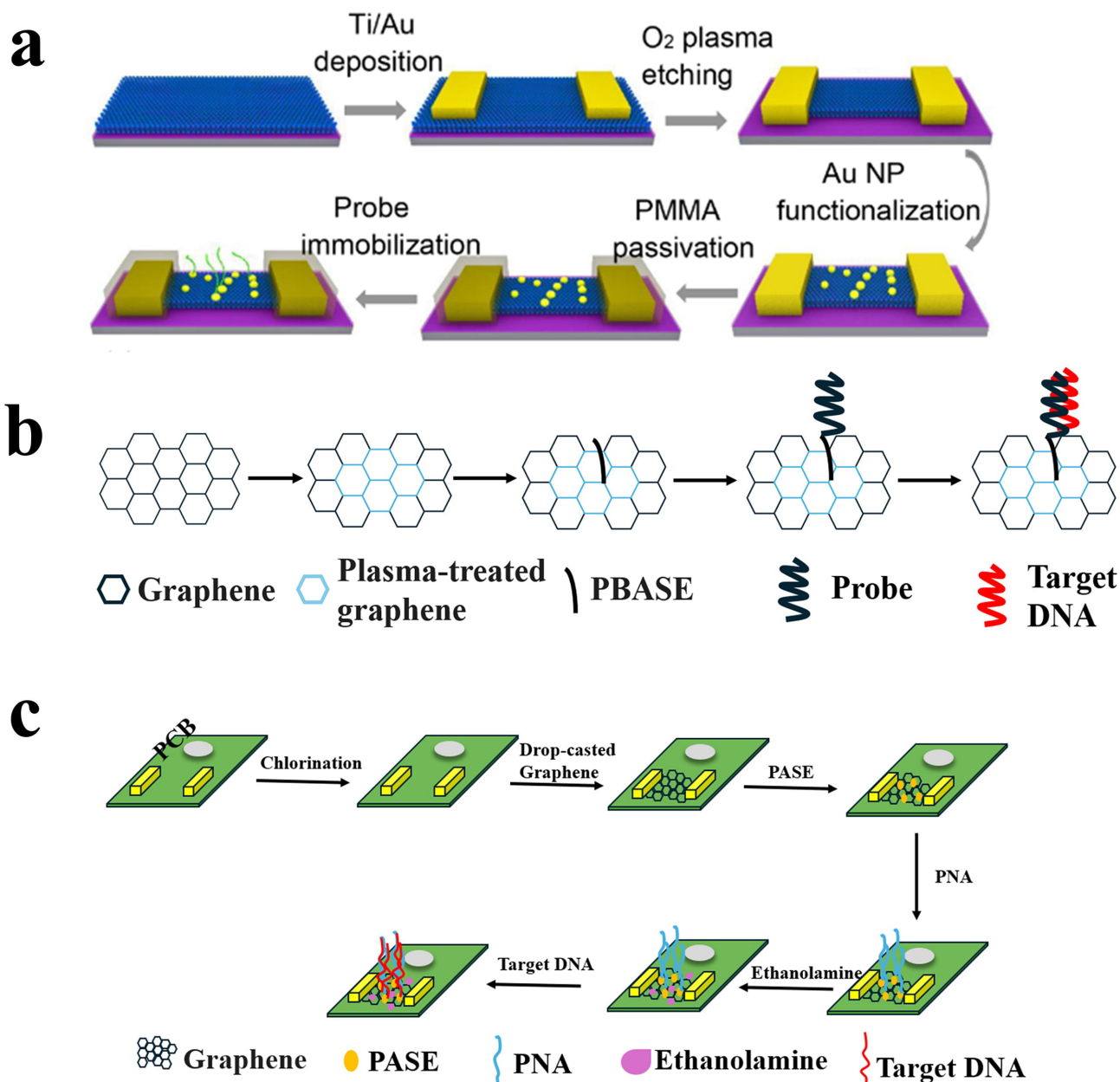


Fig. 7. Representative functionalization strategies for 2D-material FET DNA sensors. (a) Functionalization method of the ultra-sensitive MoS₂ FET DNA sensor. Reprinted with permission from Liu et al. [52]. (b) Functionalization method of the plasma-treated graphene FET DNA sensor. Based on the experimental scheme reported by Xia et al. [53]. (c) Functionalization method of the printable graphene FET sensor [55]. On MoS₂ devices treated with oxygen ions, nano gold was deposited by EBE evaporation and PMMA was spin coated, followed by the insertion of probe molecules to achieve functionalization of the device surface. Graphene undergoes plasma treatment to enhance surface activity, followed by modification of PBASE and introduction of probe molecules to achieve detection of target DNA. After re chlorination treatment on the PCB board, graphene is drop cast, and then PBASE is used to connect graphene with probe molecules to complete the functionalization of the device. PNA, peptide nucleic acid; PMMA, polymethyl methacrylate; PCB, printed circuit board.

MoS₂ nanowire FETs with DNA probes directly fixed on nanowire channels, achieving an LOD of 1 fM for hepatitis B virus (HBV) DNA in serum samples with a 25 s response time [55]. In another hybrid approach, Wang et al. [57] functionalized graphene with PBASE and immo-

bilized Cas12a-crRNA ribonucleoprotein complexes for amplification-free detection of Mycobacterium tuberculosis DNA, achieving an ultra-high sensitivity of 2.42 aM suitable for clinical sample analysis. These nanomaterial-mediated strategies share the advantage of enhanced

probe loading and improved charge transfer, but their reproducibility depends critically on the uniformity of nanoparticle deposition.

Surface activation and physical modification strategies. Physical treatments that enhance surface reactivity without introducing foreign materials offer a simpler alternative. Xia et al. [53] treated graphene with Ar plasma for 30 s to enhance hydrophilicity and remove impurities, followed by PBASE modification and probe immobilization (Fig. 7b, Ref. [53]); the plasma-treated graphene FET achieved an LOD below 10 aM for DNA hybridization in solution-gated mode, significantly outperforming untreated devices. Hwang et al. [24] proposed a folded graphene structure by transferring CVD-grown graphene onto thermoplastic materials that were thermally shrunk to create microscopic wrinkles; this wrinkled graphene liquid-gate FET achieved an LOD of 600 zM, a dramatic improvement over the 2 pM LOD of flat graphene devices [161]. Mei et al. [54] took a different approach by modifying chip channel surfaces with a positively charged layer, then depositing MoS₂ nanosheets through electrostatic interaction; phosphoramidite morpholino oligonucleotide (PMO) probes were subsequently attached for DNA hybridization detection with an LOD of 6 fM. These physical modification strategies offer the advantage of simplicity and minimal chemical interference, but the uniformity of treatment across large areas remains challenging.

Biorecognition-enhanced and printable strategies. Recent advances have leveraged specific biological recognition elements or low-cost fabrication methods. Papatmatthaiou et al. [55] used graphene ink to construct sensing channels on commercial printed circuit boards via inkjet printing, with probes fixed on graphene surfaces for target DNA identification (Fig. 7c, Ref. [55]), supporting the development of low-cost, multi-component detection systems. Tamersit et al. [58] proposed a simulation-based design using a metal–ferroelectric–metal gate structure with graphene nanoribbon channels; DNA binding increases the dielectric constant and the structure amplifies this signal, providing a concept for high-speed, label-free nucleic acid detection awaiting experimental validation in real samples. Most traditional DNA detection methods—such as polymerase chain reaction (PCR), DNA microarrays, and fluorescent labeling—involve lengthy processes and complex sample handling, making rapid on-site detection difficult [162]. Compared with these conventional techniques, 2D material FET biosensors offer label-free, amplification-free detection with rapid response. By optimizing functionalization methods and FET performance, sensitivity and selectivity can be significantly enhanced.

5.1.2 RNA Detection

In recent years, RNA detection has gained increasing attention, as RNA not only participates in gene expression regulation but also serves as an important molec-

ular marker for disease diagnosis and health monitoring. RNA molecules are inherently unstable and easily degraded, which demands rapid detection capability from sensors [163,164]. For medium- to long-chain RNA, Tian et al. [59] achieved label-free sensing using a graphene FET with peptide nucleic acid (PNA) and DNA probes, reaching an LOD of 0.1 fM with good selectivity—though real-sample validation remains lacking. Sun et al. [60] integrated Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas10 with a graphene FET by modifying gold nanoparticles on graphene channels and fixing probes via Au–S bonds; upon target RNA recognition, probe DNA is cleaved, generating an electrical signal with an LOD of approximately 427 aM and a recovery rate of 81.68–98.81% in complex samples.

miRNA detection: a focused application. miRNA—small non-coding RNA molecules (typically 19–25 nt)—has emerged as a particularly significant target due to its low abundance in body fluids and its role as a cancer biomarker [165]. Traditional miRNA detection techniques, such as qRT-PCR, require reverse transcription and amplification, adding complexity and cost [166,167]. 2D material FET biosensors offer a promising alternative for direct, label-free miRNA detection. Various functionalization strategies have been explored for miRNA-21, the most frequently studied model target. Hwang et al. [24] used a crumpled graphene field-effect transistor to detect miRNA let-7b, achieving an exceptionally low LOD of 600 zM. Huang et al. [168] prepared a layered graphene oxide/graphene (GO/G) composite via atomic layer oxidation of bilayer graphene, where the upper GO layer served as the biorecognition interface for covalent DNA probe immobilization and the lower graphene layer acted as an electron transport layer; this solution-gated graphene transistor (SGGT) achieved a detection range of 10 fM to 100 pM for miRNA-21 with good selectivity and specificity. Li et al. [62] constructed a FET biosensor using polylysine-deposited rGO with graphene quantum dot–PMO hybrids fixed through amide bonds, achieving an ultra-low LOD of 85 aM for miRNA; importantly, this method successfully differentiated plasma samples from healthy controls. Wang et al. [169] recently demonstrated an aptamer-based MoS₂ FET with high sensitivity for cytokine detection, illustrating the broader applicability of similar platforms.

Advanced functionalization strategies for miRNA detection. Beyond traditional probe immobilization, more sophisticated approaches have been developed. Xing et al. [63] prepared MoS₂ thin films via atomic layer deposition and deposited C₆₀ by vacuum evaporation to create MoS₂/C₆₀ composite channels; the photosensitive properties of C₆₀ enhance charge carrier transfer efficiency, and with AuNP-immobilized probes, the sensor achieved an ultra-low LOD of 5.16 aM for miRNA-155. Zhang et al. [64] developed a PtNWs-doped MXene-based field-effect transistor biosensor (Pt-MX-iFETs) for label-free detection of

Table 2. Representative FET biosensors based on 2D materials for nucleic acid detection.

NO	Sensor Type	Target	LOD	Reference
1	MoS ₂ FET + AuNP bridging	Chromosome 21/13 DNA fragments	<100 aM	[52]
2	Folded graphene liquid-gate FET	DNA/RNA	600 zM	[24]
3	Ar-plasma-treated graphene FET	DNA hybridization	<10 aM	[53]
4	MoS ₂ nanosheet-decorated FET (PMO probe)	DNA hybridization	6 fM	[54]
5	Inkjet-printed graphene FET	Target DNA	—	[55]
6	ZnO-doped MoS ₂ nanowire FET	HBV DNA	1 fM	[56]
7	Cas12a-functionalized graphene FET	Mycobacterium tuberculosis DNA	2.42 aM	[57]
8	Ferroelectric gate + 2D GNR FET	DNA (simulation)	—	[58]
9	Graphene FET	Medium/long-chain RNA	0.1 fM	[59]
10	CRISPR-Cas10 + AuNP-graphene FET	RNA	427 aM	[60]
11	Layered GO/G bilayer SGGT	miRNA-21	10 fM – 100 pM	[61]
12	PMO–GQD/rGO composite FET	miRNA	85 aM	[62]
13	MoS ₂ /C ₆₀ composite thin-film FET	miRNA	5.16 aM	[63]
14	PtNWs-doped MXene FET	miRNA-21	0.84 fM	[64]

FET, field-effect transistor; LOD, limit of detection; NP, nanoparticle; PMO, phosphoramidite morpholino oligonucleotide; CRISPR, clustered regularly interspaced short palindromic repeats; HBV, hepatitis B virus; GO, graphene oxide; GQD, graphene quantum dots; ATRP, atom transfer radical polymerization.

exosomal miR-21. The PtNWs@MXene architecture, with its enhanced electrical conductivity and transconductance, enabled high-affinity miRNA capture and efficient charge transfer, achieving an ultra-low LOD of 0.84 fM. Chen et al. [170] further extended 2D material FET platforms to vertical heterostructures, demonstrating the versatility of these sensing architectures.

The performance of 2D FET biosensors for nucleic acid detection depends on material properties, functionalization strategies, and probe selection. By selecting appropriate preparation methods, detection performance, stability, and selectivity can be significantly improved [54,171]. Nucleic acids—especially RNA—are easily degraded and require rapid testing after sampling. Traditional testing methods require low-temperature storage and transportation before specialized testing, resulting in high costs. The 2D material FET sensor, with its excellent electrical performance, versatile functionalization capabilities, and flexible device construction, combined with label-free detection advantages, shows broad future applications in nucleic acid detection.

Overall, recent studies on 2D material FET nucleic acid biosensors have gradually shifted from traditional DNA detection toward RNA, particularly miRNA detection. This trend is partly attributed to the fact that conventional DNA detection technologies, such as PCR and sequencing, are already highly mature, while miRNAs possess greater disease relevance and clinical significance [162,163,164]. In addition, miRNAs are relatively small molecules (typically 19–25 nt), making them more likely to remain within the Debye length compared with longer nucleic acid targets, and therefore more compatible with the electrical sensing mechanism of 2D material FET biosensors [165]. However, 2D material FET biosensors are still

strongly influenced by the intrinsic properties of the target analytes themselves. RNA molecules are inherently unstable and susceptible to degradation during sampling, storage, and detection processes, while 2D material FET biosensors cannot fundamentally eliminate RNA degradation [163,164]. In some cases, the RNA degradation process itself may even induce additional interfacial charge perturbations, further increasing signal drift and complicating signal discrimination. Maintaining RNA stability while achieving rapid detection remains one of the important challenges for future nucleic-acid-related 2D material FET biosensors.

It should be noted that although the LODs ranging from aM to zM summarized in Table 2 are technically significant, their clinical necessity warrants careful examination. For most diagnostic applications (e.g., detecting viral RNA or circulating tumor DNA), clinically relevant concentrations typically fall within the fM to pM range after sample processing. Thus, an aM-level LOD may not translate into improved outcomes compared with a sensor that offers a 100 fM LOD but exhibits superior reproducibility and stability. More critically, the literature rarely reports key practical parameters—such as reproducibility (e.g., coefficient of variation across multiple devices), batch-to-batch variation, false-positive rates due to nonspecific adsorption, or sensor lifetime during storage or continuous use. Manufacturability—the ability to produce uniform devices via scalable functionalization—remains a major gap. Addressing these practical hurdles is essential for transitioning from laboratory prototypes to reliable clinical diagnostics.

5.2 Protein Detection

Protein detection reflects the functional status and pathological changes of cells or tissues, serving as an

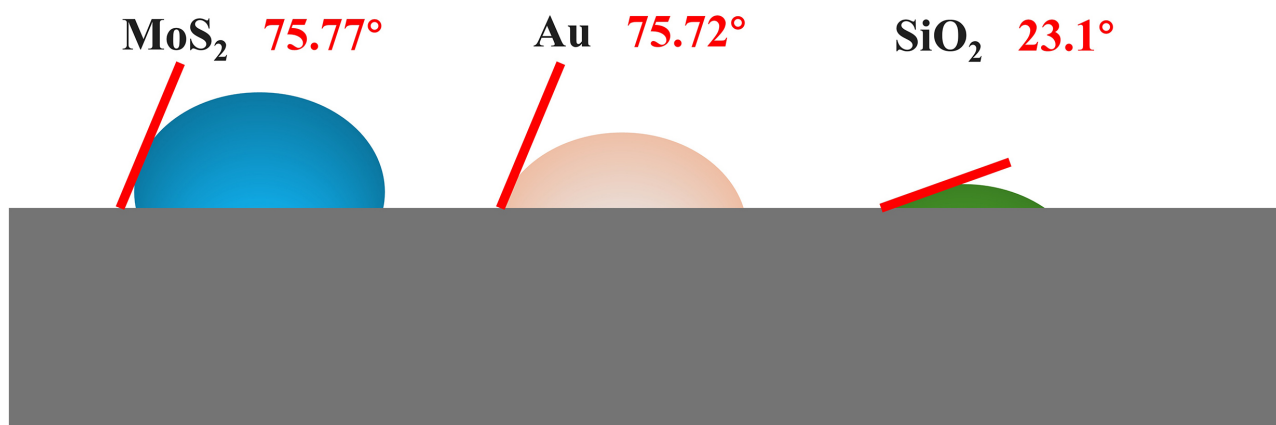


Fig. 8. Hydrophobicity comparison of substrates for biosensing applications [70]. MoS₂ and Au have a large contact angle and are suitable for direct physical adsorption of biomolecules [70,177].

important approach for discovering disease biomarkers, achieving early diagnosis, and monitoring treatment [172]. Below, we discuss representative protein targets organized by clinical relevance.

Cancer antigen-125 (CA-125). CA-125, a highly glycosylated protein encoded by the MUC16 gene, is widely used in ovarian cancer detection [173]. Ji et al. [65] detected CA-125 using an InSe FET channel with microfluidic integration; CA-125 antibodies were immobilized on the InSe surface through APTES, enabling specific capture and detection within a linear range of 0.01–1000 U/mL with a standard error below 8.78% and excellent correlation ($R^2 > 0.95$) with commercial Cobas e-601 assays. Alternatively, Mansouri Majd and Salimi developed a flexible FET-type aptasensor using rGO combined with multi-walled carbon nanotubes (MWCNT) and a CA-125 aptamer, with Polymethyl methacrylate (PMMA) as a soft substrate for wearable applications, achieving an LOD of 5.0×10^{-10} U/mL—significantly more sensitive than conventional enzyme-linked immunosorbent assay (ELISA)/chemiluminescent enzyme immunoassay (CLEIA) (LOD ≈ 1 –2 U/mL) and simpler to operate [67,174]. The comparison between antibody-based (InSe/APTES) and aptamer-based (rGO/MWCNT) strategies illustrates a general trade-off: antibodies offer established specificity but require careful orientation control, while aptamers provide simpler immobilization and greater flexibility for wearable formats.

Prostate-specific antigen (PSA) is a serine protease and a key biomarker for prostate cancer screening and monitoring [175]. Several functionalization strategies have been compared for PSA detection. Song et al. [68] used vertically aligned MoS₂ nanolayers (VAMNs) as FET channels, exploiting the strong affinity between 11-mercaptoundecanoic acid and VAMNs for label-free PSA detection, achieving an LOD of 800 fg/mL (≈ 0.027 pM) in human serum with a 20-min response time—over ten times more sensitive than commercial ELISA (≈ 8 pg/mL) [176].

Kong et al. [69] developed a graphene FET using PBASE for stable aptamer immobilization, achieving a 3.5 pM LOD and recovery rates of 97.2–100.1% in serum samples. In a simpler approach, Lee et al. [70] directly immobilized anti-PSA antibodies on MoS₂ channels through physical adsorption, taking advantage of the hydrophobic MoS₂ surface (contact angle 75.77°, comparable to Au and significantly higher than hydrophilic SiO₂, as shown in Fig. 8, Ref. [70,177]) to facilitate spontaneous protein adsorption; the LOD reached 1 pg/mL (≈ 0.033 pM), well below the clinical cutoff of ≈ 4 ng/mL. Mandal et al. [71] developed a label-free graphene FET sensor integrated with a compact disc-based microfluidic platform for PSA detection at the point of care. The device achieved a detection limit of 1 pg/mL in serum with a dynamic range up to 4 ng/mL and was validated using human serum samples. These results collectively show that while direct physisorption is the simplest route, the more controlled covalent or PBASE-mediated immobilization offers better reproducibility and stability for quantitative clinical use.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike protein. The SARS-CoV-2 Spike glycoprotein, exposed on the viral surface, is the primary target for immune recognition and vaccine development [178]. Sousa et al. [72] developed a graphene FET with monoclonal antibody functionalization, achieving an LOD of 1 fg/mL in serum within 100 μ s using a short gate voltage pulse. Fathi-Hafshejani et al. [20] utilized single-layer WSe₂ FETs with 11-mercaptoundecanoic acid (MUA) self-assembled monolayers: the -SH end of MUA interacts with sulfur vacancies on WSe₂, and the carboxyl end is activated by NHS-EDC to covalently link antibodies via amide bonds, achieving an LOD of 25 fg/ μ L in 0.01 $\times$ PBS. Romagnoli et al. [73] modified graphene with PBASE to immobilize an engineered dimeric angiotensin-converting enzyme 2 (ACE2)-Fc protein that specifically binds the Spike protein, achieving an LOD of 20 pg/mL for recombinant Spike and 65 cps/mL for swab

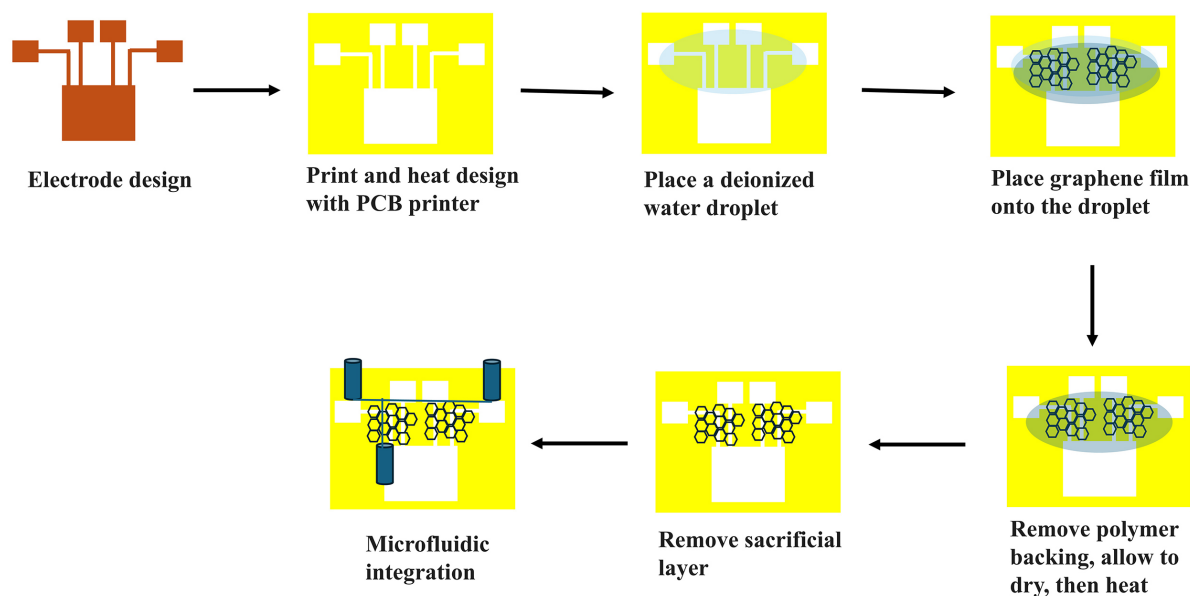


Fig. 9. Fabrication process flow of the GFET device. Based on the experimental scheme reported by Laliberte et al. [182]. This device is prepared by using PCB printed electrodes, transferring graphene with the assistance of deionized water, drying, and removing the sacrificial layer.

samples, with potential adaptability to viral mutations. The ACE2-based strategy offers the advantage of broader recognition across viral variants compared to antibody-based approaches.

Interleukin-6 (IL-6) and cardiac troponin I (cTnI). IL-6 is a glycoprotein indicating inflammation levels and is used to monitor treatment efficacy and disease progression [179,180,181]. Hao et al. [74] used PBASE as a bridge between graphene channels and IL-6 aptamers, achieving detection within 10 minutes and an LOD of 139 fM after 24 h ambient storage, indicating good stability. In a more elaborate design, Wang et al. [66] used PBASE for π - π stacking on graphene, connected the other terminal to polyethylene glycol, activated the carboxyl PEG chain with EDC/NHS, and covalently linked amino-modified aptamers, achieving an LOD of 0.20 pM for IL-6. Inkjet-printed liquid-gated devices with IL-6 aptamers achieved an LOD of 372 pM in 1×PBS [75]. Laliberte et al. [182] developed a wearable graphene field-effect transistor (GFET) sensor using a conductive-ink-based printed circuit board (PCB) printer with PBASE-connected aptamers (Fig. 9, Ref. [182]), achieving a sensing range of 10 pM to 100 nM; the bending curvature radius of 1.5–4.25 cm makes it suitable for wearable device fabrication. For cTnI, Huang et al. [76] immobilized yolk-shell structured plasmonic nanoparticles modified with anti-cTnI antibodies on MoS₂ FET channels; the nanostructures expanded the effective reaction interface and enhanced recognition efficiency, requiring only 20 μ L of sample to achieve an LOD of 2.66 pg/mL ($\approx$ 0.11 pM) with strong anti-interference capability.

Compared with the nucleic-acid-related 2D material FET biosensors summarized in Table 2, the

protein-detection-related biosensors listed in Table 3 generally exhibit higher limits of detection [59,62,63,168,169,170,183,184]. This may be associated with the intrinsically more complex structural characteristics of proteins. Compared with nucleic acids, proteins usually possess larger molecular sizes, more complicated three-dimensional conformations, and heterogeneous surface charge distributions [172,179]. As a result, the charge perturbations induced by target protein binding are more likely to occur beyond the Debye length, thereby weakening the effective electrical coupling between biomolecules and the sensing channel. In addition, protein sensing is more susceptible to nonspecific adsorption, protein fouling, and interface signal drift [74,169]. In complex biological samples, some proteins may directly adsorb onto the surface of 2D material channels and generate additional electrical signals even without specific recognition, thereby increasing the risk of false-positive signals [66,169]. Most of these issues are not unique to 2D material FET biosensors, but represent common challenges in protein sensing in general. Compared with nucleic acid detection, protein sensing usually places higher requirements on antifouling interfaces, functionalization stability, and selective recognition strategies.

Notably, the LODs achieved for protein targets (Table 3) are generally higher (pM to fM range) than those for nucleic acids (aM to fM). This partially reflects intrinsic protein properties, but also the fact that the clinically required sensitivity for proteins is less demanding. For PSA, the clinical cutoff is $\approx$ 130 pM; sensors with an LOD of 1 pg/mL ($\approx$ 0.033 pM) already offer more than adequate sensitivity. Further improvements in LOD yield

Table 3. Representative 2D material FET biosensors for protein detection.

NO	Sensor Type	Target Protein	LOD	Reference
1	InSe FET + microfluidic + APTES	CA-125	0.01–1000 U/mL	[65]
2	rGO/MWCNT FET + aptamer	CA-125	5.0×10^{-10} U/mL	[67]
3	VAMNs–MoS ₂ vertical nanosheet FET	PSA	800 fg/mL (~0.027 pM)	[68]
4	Graphene FET + PBASE aptamer	PSA	3.5 pM	[69]
5	MoS ₂ FET + physisorbed antibody	PSA	1 pg/mL (~0.033 pM)	[70]
6	Microfluidic graphene FET	PSA	1 pg/mL (~0.033 pM)	[71]
7	Graphene FET + monoclonal antibody	SARS-CoV-2 Spike	1 fg/mL (~0.000013 pM)	[72]
8	WSe ₂ FET + MUA–NHS/EDC	SARS-CoV-2 Spike	25 fg/ μ L (~0.33 pM)	[20]
9	Graphene FET + ACE2-Fc (PBASE)	SARS-CoV-2 Spike	20 pg/mL (~0.27 pM)	[73]
10	Graphene FET + PBASE aptamer	IL-6	139 fM	[74]
11	Graphene FET + PBASE–PEG–aptamer	IL-6	0.20 pM	[66]
12	Inkjet-printed liquid-gated GFET + aptamer	IL-6	372 pM	[75]
13	Wearable GFET + PBASE aptamer	IL-6	10 pM–100 nM	[75]
14	MoS ₂ FET+ nanostructure	cTnI	2.66 pg/mL (~0.11 pM)	[76]

Note: Concentrations reported in pg/mL or fg/mL have been approximately converted to molar units (pM) for comparison. The conversions assume molecular weights of PSA (~30 kDa), SARS-CoV-2 Spike protein (~75 kDa), IL-6 (~21 kDa), and cardiac troponin I (cTnI, ~24 kDa). Concentrations originally reported in U/mL are activity units and are therefore not converted to molar units.

CA, cancer antigen; APTES, (3-Aminopropyl)triethoxysilane; MWCNT, multi-walled carbon nanotubes; VAMNs, vertically aligned MoS₂ nanolayers; PSA, prostate-specific antigen; PBASE, 1-pyrenebutanoic acid succinimide ester; SARS, severe acute respiratory syndrome; MUA, 11-mercaptopundecanoic acid; NHS, N-hydroxysuccinimide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; GFET, graphene field-effect transistor; PEG, polyethylene glycol.

diminishing clinical returns. Instead, for protein detection in real-world settings, reproducibility and fouling resistance become paramount. Proteins readily adsorb non-specifically to 2D surfaces, causing baseline drift and false positives [56]. Few studies validate performance in undiluted, untreated clinical samples; most rely on spiked buffer or diluted serum. Sensor lifetime under continuous or repeated use, batch-to-batch consistency, and manufacturability (e.g., uniform antibody immobilization) are rarely systematically reported. Adopting standardized protocols for these metrics would greatly enhance translational relevance.

5.3 Peptide Detection

Peptide hormones are important signaling molecules composed of amino acids, with concentrations typically at the pM–fM level. Even small changes can reflect the body's metabolism and growth status. Timely and convenient peptide hormone detection technologies are of great significance for daily health monitoring and disease prevention [161,185]. Compared to traditional electrochemical or optical methods, 2D material FET can achieve real-time dynamic monitoring and has the advantages of integration and miniaturization, making it particularly suitable for emerging directions such as biomedical sensing, wearable diagnostics, and multi-component biological analysis [21,186]. Several biosensors for detecting peptides are summarized in Table 4. Ahn et al. [77] developed graphene FET sensors using nanovesicles that formed π –

π stacking with the graphene surface via 1-pyrenebutanoic acid N-hydroxysuccinimide ester; the active ester end reacted with amino groups on vesicles, enabling directional fixation of receptor-carrying nanovesicles. Charge variations from hormone–receptor binding generated highly sensitive responses, with LODs of 100 fM for parathyroid hormone and 1 pM for glucagon. Chen et al. [78] used chitosan and glutaraldehyde crosslinking to immobilize anti-procalcitonin (PCT) antibodies on GFET channels; PCT binding affected graphene carrier concentration, altering FET conductivity with an LOD of 0.82 ag/mL in PBS, suitable for rapid clinical screening. Hao et al. [79] functionalized graphene with a guanine-rich IGA3 aptamer via PBASE adsorption through π – π interactions; the aptamer was connected through amide bonds, and insulin binding changed graphene conductivity, achieving label-free detection with an LOD of 35 pM.

Although peptides are relatively small molecules, they are generally less stable than nucleic acids. Peptides are susceptible to enzymatic degradation, oxidation, adsorption loss, aggregation, and conformational variation during sampling, storage, and detection processes. Previous peptide assay studies have pointed out that pre-analytical handling may critically influence the reliability of peptide detection results [185]. To improve sensing stability, several studies have explored different strategies, including constructing receptor-carrying nanovesicles to preserve the native membrane environment of G protein-coupled receptors (GPCRs), as well as employing chitosan, crosslink-

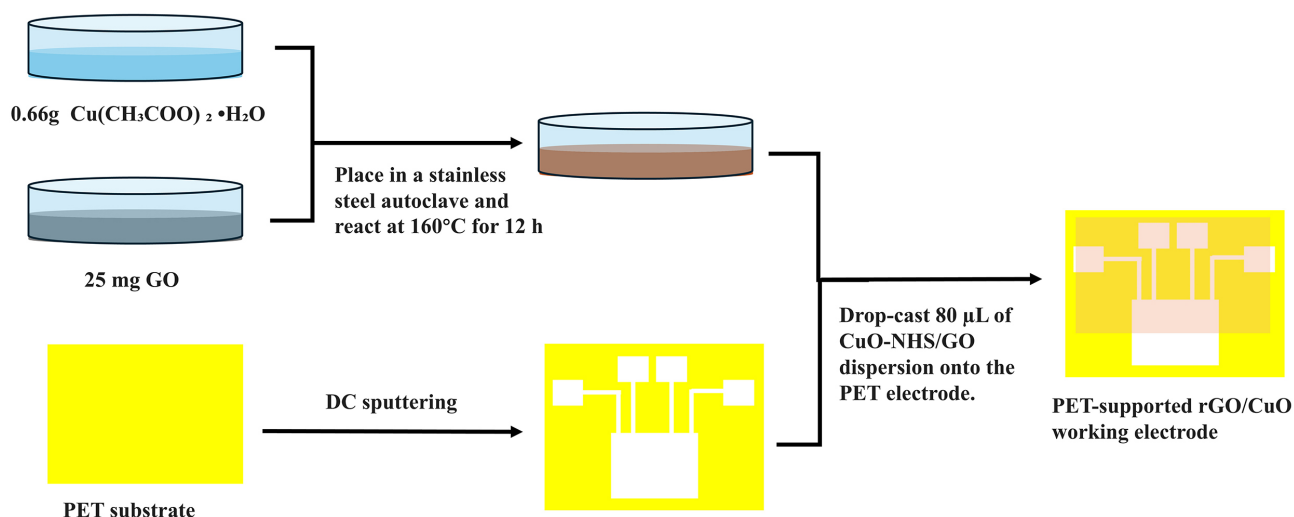


Fig. 10. Schematic of the rGO/CuO–NHS BGFET sensor synthesis and fabrication process [80]. GO is reduced to rGO during the CuO hollow sphere process, and the binding of rGO to CuO can detect the efficiency and selectivity of glucose. BGFET, back-gate field-effect transistor.

Table 4. Representative 2D material FET biosensors for peptide and saccharide detection.

NO	Sensor Type	Target	LOD	Reference
1	Graphene FET + PBASE aptamer	Parathyroid hormone	100 fM	[77]
2	Graphene FET + PBASE aptamer	Glucagon	1 pM	[77]
3	Graphene FET + chitosan/glutaraldehyde crosslinking	PCT (Procalcitonin)	0.82 ag/mL	[78]
4	Graphene FET + PBASE aptamer	Insulin	35 pM	[79]
5	rGO/CuO hollow microsphere FET + aptamer	Glucose	1 nM	[80]
6	Wearable MXene-based paper FET	Glucose	10 nM	[81]
7	Graphene FET with microwave transmission	Glucose	5 µM	[82]

ing layers, or PBASE-based interface modification strategies to enhance the immobilization stability of antibodies or aptamers on 2D material surfaces [78,79]. In addition, aptamer-based strategies have attracted increasing attention because smaller recognition elements are more likely to remain within the Debye length [79]. For 2D material FET biosensors, these issues may become even more pronounced because FET sensing strongly depends on stable interface charge coupling. In some cases, peptides may already undergo conformational variation during the binding process, resulting in unstable electrical responses and increased difficulty in signal discrimination. Therefore, besides further improving sensing sensitivity, maintaining peptide stability and reliable interface interactions remains one of the major challenges for practical peptide-related 2D material FET biosensors. For peptide and saccharide sensors (see Table 4), the gap between reported LODs (often fM to pM) and clinically relevant levels (pM to nM for hormones, mM for glucose) is narrower. For glucose, the clinical priority is not ultralow sensitivity but rather long-term stability, drift-free operation, and biofouling resistance during continuous monitoring. Hence, sensor lifetime and reproducibility are far more critical than further lowering the LOD.

5.4 Saccharide Detection

2D material FET biosensors have become a research hotspot in saccharide detection, mainly focusing on glucose for blood sugar monitoring and diabetes management [187]. Several biosensors for detecting saccharides are summarized in Table 4. Farahmandpour et al. [80] developed a glucose biosensor using a back-gated FET with rGO/CuO hollow-microsphere channels (Fig. 10, Ref. [80]), achieving an LOD of 1 nM with good repeatability; after two weeks, it retained 93% of initial response and showed good selectivity against common blood interferents. The same group later developed a wearable, paper-based FET biosensor for continuous sweat glucose monitoring, using poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) ink electrodes, a polydimethylsiloxane (PDMS) dielectric layer, and CuO-adsorbed Ti₃C₂ MXene as the channel material, achieving an LOD of 10 nM [81]. Gubeljak et al. [82] combined microwave transmission with graphene FET biosensors, utilizing physical adsorption of glucose molecules at microwave frequencies for rapid detection with an LOD of 5 µM; this method requires no enzymes or dyes and shows strong resistance to chemical interference. While glucose dominates saccharide sensing due to its clinical demand, simple structure, and

mature recognition systems, research on other saccharide remains limited [80,81,82,187]. For glucose, the clinical priority is not ultralow sensitivity but rather long-term stability, drift-free operation, and biofouling resistance during continuous monitoring—a perspective we expand upon in Section 5.

Comparing the four target classes reveals that the choice of functionalization strategy strongly depends on analyte size and sample complexity. For small nucleic acids (miRNA), direct covalent attachment with short linkers or hybrid π - π stacking plus amide bonding works well, keeping the recognition layer thin to mitigate Debye screening. For proteins, additional antifouling layers (e.g., PEG, hydrogels) are often necessary to reduce nonspecific adsorption, but these layers increase the probe-channel distance, potentially attenuating signals. Peptide detection benefits from preserving native receptor conformation (e.g., nanovesicles) or using aptamers. Glucose detection relies on enzymatic or affinity-based recognition, where long-term stability and drift are more important than LOD. Overall, no single functionalization strategy fits all targets; the design must be tailored to the specific analyte and intended application environment.

6. Future Prospects of 2D Material FETs

Traditional biomolecule detection methods often rely on complicated sample pretreatment, chemical labeling, and time-consuming experimental procedures, which limit their applicability for rapid and real-time monitoring. Benefiting from label-free electrical detection and rapid signal response, 2D material-based FET biosensors exhibit great potential for highly sensitive biomolecule detection [1,188,189]. However, practical applications of 2D material FET biosensors in real biological samples still face substantial challenges. One of the most important limitations is the Debye screening effect, where excess ions in high-ionic-strength biological environments screen the electrical signals generated by target molecules, thereby weakening the effective electrostatic coupling between biomolecules and the sensing channel [157,189]. As a result, many FET biosensors demonstrate excellent sensitivity in low-ionic-strength buffer systems, while their sensing performance often decreases significantly in real biological samples such as serum, saliva, and sweat. In several examples discussed in Section 4, the detection signals obtained from practical samples were noticeably lower than those measured in buffer systems.

Therefore, current practical applications often require a compromise between sensing sensitivity and sample pretreatment complexity. In many cases, sample dilution, desalting, or removal of interfering substances is still necessary to reduce ionic strength. Since Debye screening is difficult to completely eliminate under physiological conditions, current strategies mainly focus on partially alleviating its influence. To alleviate the Debye screening effect, sev-

eral strategies have recently been explored. At the interface level, shortening probe length and using smaller recognition elements such as aptamers or peptides can help ensure that charge perturbations induced by target binding remain within the Debye length. At the device level, optimization of local electric field structures, introduction of nanogap or nanostructured architectures, and dual-gate designs have been employed to enhance local signal modulation and improve sensing sensitivity [190,191]. Although several recent studies have attempted to achieve biosensing beyond the Debye length limitation, realizing stable, highly sensitive, and long-term reliable detection under realistic physiological environments is still difficult in current practical systems [192].

In addition to the Debye screening effect, which is a common limitation for most 2D material FET biosensors, different practical application scenarios may introduce even more complex challenges. For example, in multiplex sensing applications, the ultrathin structure and excellent integrability of 2D materials enable differently functionalized sensing units to be integrated onto the same chip for high-throughput detection [193,194,195]. However, increasing integration density may also introduce electrical crosstalk, local ionic environment variation, and signal interference among adjacent sensing channels, thereby affecting detection accuracy. In addition, nonspecific adsorption, cross-reactivity among different functionalized interfaces, and protein fouling in complex samples may further complicate multiplex signal analysis [196]. At present, most multi-channel 2D material FET biosensors still remain at the laboratory prototype stage, while long-term stable operation in realistic biological samples is still rarely reported.

For wearable and implantable applications, 2D material FET biosensors must not only achieve flexibility and low-power operation, but also maintain long-term stable performance under complex and dynamic physiological environments [197,198]. During long-term operation, devices may be affected by repeated mechanical deformation, biofluid exposure, protein fouling, and immune responses, resulting in signal drift and reduced sensing stability. In addition, to preserve device flexibility, thinner encapsulation layers and flexible substrates are often employed, which may further compromise long-term environmental stability and durability. Therefore, maintaining long-term stability and biosafety while preserving mechanical flexibility continues to limit practical wearable and implantable applications of 2D material FET biosensors. Although 2D material FET biosensors exhibit advantages of low operating voltage and low power consumption, long-term implantable sensing systems still require stable energy supply to maintain continuous signal acquisition, wireless data transmission, and real-time signal processing. Recent studies have demonstrated the feasibility of self-powered biosensing systems. For example, Wang et al. [199] developed a triboelectric nanogenerator (TENG)-driven self-

powered biosensing system capable of operating without an external power supply. Such strategies may provide new opportunities for future implantable 2D material FET biosensors, because FET devices themselves exhibit low operating voltage and low power consumption characteristics, making them more suitable for stable operation in long-term biological environments and *in vivo* biosafety requirements. However, compared with conventional sensing platforms, self-powered and wireless biosensing systems are still relatively limited. Simultaneously maintaining stable energy output, device miniaturization, wireless communication reliability, and long-term operational stability, particularly in implantable systems requiring continuous monitoring, is still not fully resolved for current 2D material FET biosensors [200].

For portable sensing applications, 2D material-based FET biosensors exhibit advantages including miniaturization, low-power operation, and rapid detection [201]. Compared with laboratory conditions, practical portable sensing is more susceptible to environmental factors such as temperature fluctuation, humidity variation, and external electrical noise, which may result in sensing instability and signal variation. In addition, sample composition under real-world conditions may vary significantly, including differences in pH, ionic strength, and complex background components, further increasing the complexity of quantitative analysis and data processing. Meanwhile, cost also remains an important limitation for portable applications. Some current 2D material FET biosensors are still difficult to reuse, and replacement of the functionalized interface or even the entire substrate may be required after detection, thereby increasing operational cost. To improve reusability, several studies have explored reversible self-assembled interfaces, dynamic functionalization layers, and regenerable sensing interfaces [202,203], although these approaches also place higher requirements on functionalization stability and controllability. In addition, low-cost flexible platforms such as paper-based graphene devices have recently attracted attention for reducing sensing cost and improving practical applicability [204]. Nevertheless, maintaining stable and reliable sensing performance under complex environments while simultaneously achieving low cost and reusability remains one of the major challenges for portable applications of 2D material FET biosensors.

Beyond the performance metrics discussed above, several practical production and regulatory challenges must be addressed before 2D material FET biosensors can be commercialized, especially for wearable and implantable applications. (1) Wafer-scale synthesis and uniformity. While laboratory-scale devices often use exfoliated flakes or small-area CVD growth, industrial production requires wafer-scale (e.g., 4- or 6-inch) growth of high-quality 2D materials with controlled layer number, minimal defects, and uniform electrical properties [12]. Variability in grain boundaries, thickness, and doping across a wafer directly

translates into device-to-device variations in baseline current, Dirac point, and sensitivity [205]. (2) Packaging and interconnection. FET biosensors require electrical connections to readout electronics while maintaining a stable liquid interface for biological sampling. For implantable or wearable devices, packaging must protect the 2D material and functionalization layer from moisture, ions, and mechanical stress, yet still allow target analyte access to the sensing surface [206]. This “biofluid-compatible packaging” is nontrivial; leakage, delamination, and corrosion of contact electrodes are frequent failure modes [207]. (3) Calibration drift and device aging. Even well-functionalized devices exhibit baseline drift over time due to gradual changes in the 2D material surface (oxidation, doping), linker degradation, or probe denaturation [208,209]. Drift is exacerbated under continuous operation or repeated use. Calibration strategies (e.g., on-chip reference electrodes, differential sensing, or periodic recalibration) are rarely integrated into current prototypes. Aging studies (accelerated aging under elevated temperature/humidity, or real-time aging over months) are seldom reported, yet they are essential for predicting shelf life and operational lifetime [210]. (4) Regulatory hurdles (FDA, CE, etc.). For clinical diagnostic use, biosensors must meet regulatory standards for safety, efficacy, and quality control. This requires validated manufacturing processes, documented reproducibility across multiple batches, stability testing, and clinical validation in prospective trials [29]. The novelty and variability of 2D material functionalization pose challenges for quality assurance. Regulatory agencies currently lack standardized testing protocols specifically for 2D material FET biosensors, creating uncertainty for commercial development. (5) Integration with readout and wireless systems. For wearable and implantable applications, the sensor must be integrated with low-power, miniaturized electronics for signal amplification, analog-to-digital conversion, and wireless data transmission [211]. This integration adds complexity to packaging and calibration and introduces additional sources of noise and drift [212]. These production and regulatory challenges are not insurmountable, but they are often underestimated in academic literature. Future research should focus not only on improving sensitivity but also on developing solutions for scalable manufacturing, robust packaging, long-term calibration stability, and regulatory compliance. Collaborative efforts among materials scientists, process engineers, packaging specialists, and regulatory experts will be essential to bridge the gap from laboratory demonstrations to commercially viable products.

Building on the above production challenges, device uniformity deserves special emphasis. Furthermore, when transitioning from laboratory demonstrations to industrial-scale production, device uniformity remains a critical challenge for 2D material FET biosensors. Variations in material synthesis, transfer, and functionalization processes can easily introduce defects, contamination, wrinkles, and in-

interface residues, resulting in significant device-to-device variation in baseline current, Dirac point position, and sensing sensitivity. Although normalization methods such as I/I_0 are commonly employed to reduce device variation, differences in intrinsic noise, signal drift, and interface conditions still make reproducible sensing difficult to achieve. Current approaches to improve reproducibility include wafer-scale CVD growth, standardized transfer processes, annealing treatments, reference-channel calibration, and integration of advanced data analysis or machine-learning-assisted correction methods [213]. Nevertheless, achieving highly uniform large-scale production of 2D material FET biosensors remains highly challenging.

Overall, although 2D material-based FET biosensors still face many challenges in practical applications, including Debye screening, long-term stability, device reproducibility, and large-scale manufacturing, their unique advantages in label-free detection, ultrahigh sensitivity, miniaturization, flexibility, and system integration still make them promising for future biosensing applications. With recent advances in material synthesis, interface engineering, flexible electronics, and data analysis methods, 2D material FET biosensors are expected to gradually move from laboratory demonstrations toward more reliable practical applications in healthcare monitoring, wearable electronics, and precision medicine [214,215]. In addition, it should be noted that many current studies still focus heavily on achieving increasingly lower LOD values, and some 2D material FET nucleic acid biosensors have already reached aM- or even zM-level detection limits. However, for many practical biomarkers, clinically relevant concentrations are often significantly higher than these ultralow detection limits [216]. Therefore, rather than continuously pursuing extremely low LOD values, future studies may need to place greater emphasis on stability, reproducibility, long-term reliability, and standardized detection performance in complex real biological samples, thereby promoting the practical clinical translation of 2D material FET biosensors [217].

Author Contributions

CD is responsible for the revision of the paper and the acquisition of funds, and participates in the collection and analysis of data. BG participates in writing the first draft and conceptualization. ZW and YH participated in writing the first draft of the paper, collecting documents and analyzing data. AA participated in writing the first draft of paper and polishing the article, and participated in data processing. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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