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Advanced Materials for Biological Field-Effect Transistors (Bio-FETs) in Precision Healthcare and Biosensing

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Biological Field Effect Transistors (Bio-FETs) are redefining the standard of biosensing by enabling label-free, real-time, and extremely sensitive detection of biomolecules. At the center of this innovation is the fundamental empowering role of advanced materials, such as graphene, molybdenum disulfide, carbon nanotubes, and silicon. These materials, when harnessed with the downstream biomolecular probes like aptamers, antibodies, and enzymes, allow Bio-FETs to offer unrivaled sensitivity and precision. This review is an exposition of how advancements in materials science have permitted Bio-FETs to detect biomarkers in extremely low concentrations, from femtomolar to attomolar levels, ensuring device stability and reliability. Specifically, the review examines how the incorporation of cutting-edge materials architectures, like flexible / stretchable and multiplexed designs, is expanding the frontiers of biosensing and contributing to the development of more adaptable and user-friendly Bio-FET platforms. A key focus is placed on the synergy of Bio-FETs with artificial intelligence (AI), the Internet of Things (IoT), and sustainable materials approaches as fast-tracking toward transition from research into practical healthcare applications. The review also explores current challenges such as material reproducibility, operational durability, and cost-effectiveness. It outlines targeted strategies to address these hurdles and facilitate scalable manufacturing. By emphasizing the transformative role played by advanced materials and their cementing position in Bio-FETs, this review positions Bio-FETs as a cornerstone technology for the future healthcare solution for precision applications. These advancements would lead to an era where material innovation would herald massive strides in biomedical diagnostics and subsume.

1. Introduction

Field-effect transistors (FETs) are among the foundation stones of modern electronics, widely used in communication, computation, and sensing technologies.[1,2] Their inherent ability to modulate electrical signals has been instrumental to drive advancements of electronic and biosensing device functionality and integration. [3,4] In recent years, the adapation of FETs to biological applications - known as biological FETs (Bio-FETs) - has emerged as powerful platform in biosensing, enabling real-time detection of biomarkers with high sensitivity an selectivity.

Initially, due to more established fabrication techniques and better stabilized electrical properties, Bio-FETs were built from silicon-based semiconductors.[5–7] These materials were limited because of their low surface functionalization capability, reduced sensitivity because of bulk charge transport, and interference caused by electrolyte solutions.[8,9] To overcome the abovementioned challenges, other materials were studied, which led to significant advances in Bio-FET technologies. With the arrival of organic semiconductors at the end of 1990, not only did they provide better biocompatibility but also gave rise to flexible biosensing devices.[10] However, their reduced charge carrier mobility

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limited their overall performance in real-time detection applications. The 2000s witnessed the rise of a major breakthrough in Bio-FET development due to the appearance of carbon-based nano-materials, such as carbon nanotubes and graphene.[11,12] With remarkable surface-to-volume ratios, higher charge carrier mobility, and label-free detection capabilities, these materials provided considerable improvements in biosensing performance.[13,14]

More recently, research into Bio-FET technology has also advanced with the integration of 2D materials, such as molybdenum disulfide (MoS_2), black phosphorus, or MXenes, among others.[15–17] They are mechanistically ultrathin materials, which means they could provide great charge modulation and, therefore, improved sensitivity in the detection of biomolecular interactions. Recently developed tunable electronic properties and better stability in physiological environments make 2D materials among the most promising candidates for incorporation into next-generation real-time diagnostic applications.[18–20] Innovations via these materials has been improving the Bio-FET detection performance by a variety of fundamental mechanisms: 1) increased surface-to-volume ratios heightening the charge interactions and lowering the detection limits; 2) enhancing the charge carrier mobility, thus increasing analyte response times; 3) improving biocompatibility with better functionalization, though with less need for complicated surface modifications; and 4) diminishing interference effects, and, thereby, enhancing the signal-to-noise ratio in biosensing measurements. By taking advantage of these innovations, Bio-FETs have matured into very advanced biosensors to detect an extensive range of biomolecules with incredible accuracy and in record time.[21–23]

Bio-FETs present several key advantages over electronic components such as Bipolar Junction Transistors (BJTs) and resistors when comes to biosensing applications. High input impedance allows Bio-FETs to capture minute modifications in charge distributions due to biomolecular interactions, which is one of their key attributes for this purpose. Unlike BJTs that make use of current amplification to control conduction and, thus, require a continuous supply of base current, Bio-FETs are operated through voltage-controlled conduction.[24] This makes them sensitive to the electrostatic environment introduced by biomolecules, which is very useful in a label-free detection mode, allowing near real-time sensing with no additional reagents or complex labeling required. Another attractive aspect of Bio-FETs relates to their fast response time and low power consumption. Since they directly transduce biochemical interactions into measurable electrical signals, Bio-FETs do not need signal amplification, as it is the case with resistive sensors that work on changes in resistance.[25] Such scalability of Bio-FET technology provides opportunities for ultrasensitive detections down to a single-molecule level. Their small size and compatibility with CMOS technology allow them to be integrated into portable and miniaturized biosensing platforms, enhancing their practicality for point-of-care diagnostics. Similarly, the electrostatic gating mechanism in Bio-FETs provides an intrinsic advantage against conventional resistive sensors since their presence induces a shift in threshold voltage or drain current, allowing highly selective and specific detection. Conversely, BJTs are still thermally unstable due to inherent base current fluctuations, while Bio-FETs exhibit higher operational stability and reproducibility in biosensing environments.[26,27]

In light of these distinctive capabilities, Bio-FETs are not merely incremental improvements but represent a paradigm shift in the design and functionality of biosensing technologies, offering a seamless interface between biological recognition and electronic signal transduction. Bio-FETs merge the semiconductor-based structure of conventional FETs with biological recognition elements, such as but not limited to enzymes, antibodies, or nucleic acids, enabling real-time, label-free detection of biomolecules. This transformative capability opens avenues for applications in healthcare, environmental monitoring, and beyond. As healthcare and related environmental sectors increasingly demand rapid, precise and decentralized diagnostic tool,[28,29] Bio-FETs stand at the intersection of biological recognition and electronic signal processing. Their technological versatility, empowered with advanced materials, position themselves as a transformative platform for next-generation. biosensing and precision healthcare.[30–32]

Bio-FETs work by directly electronically detecting biological interactions instead of traditional methods that mostly depend on molecular labeling techniques.[33] This characteristic simplifies the analytical procedure and shortens assay completion time.[34,35] For example, glucose-sensing, enzyme-functionalized FETs (ENFETs) have developed diabetes management; DNA-functionalized FETs (DNA-FETs) are pushing personalized medicine forward, thanks to genetic analysis.[36] Immuno-FETs, taking advantage of antigen–antibody interactions, are changing the detection of cancer- or infectious-disease-related biomarkers. Rooted in the technology of Bio-FETs are the materials from which they derive their powers. The contribution of advanced materials, such as graphene, molybdenum disulfide (MoS_2), carbon nanotubes (CNTs), and other 2D materials, in advancing the capacities of Bio-FETs is worth noting.[37,38] These materials confer high surface-to-volume ratios, outstanding electric conductivity, and mechanical flexibility, which are crucial for achieving ultralow detection limits and operational stability in complex biological environments.[6,39]

The use of nano- and micro-structures, such as nanoparticles and polymers, in the functionalization of Bio-FET surfaces improve sensitivity and specificity.[40,41] Functionalized surfaces enhance the binding efficiency of biomolecules and minimize nonspecific interactions that, in turn, decrease noise and increase signal-to-noise ratios.[27] For instance, functionalization with aptamers or antibodies enables selective detection of target analytes, while surface modifications with biocompatible coatings are known to increase device stability in biological environments.[40,42] Despite impressive advancements, Bio-FET material development still features several challenges. These include reproducible signal transduction, long-term stability, and scalability issues.[43,44] Many of the challenges that arise from ionic interference in biological fluids often disregard signal transduction via Bio-FETs. Ionic screening effects and nonspecific binding would often impede various sensor performances. Therefore, innovative material designs such as hybrid organic–inorganic interfaces and nanostructured surfaces are being developed to mitigate these challenges.[45] Crafting Bio-FETs with mass-producible properties would unquestionably present another barrier. Such production alike shall involve sophisticated materials like graphene and MoS_2 with the guarantee of precise regulation of both material quality and device ar-

chitecture. In addition, compatibility with the complementary metal–oxide–semiconductor (CMOS) process should be guaranteed for commercialization. Balancing performance against mass-producibility would remain a primary center of attention for Bio-FET research.[46]

Our review presents a comprehensive, material-centric analysis of Bio-FETs that distinguishes it from previous works by offering a broader perspective on advanced materials, their impact on biosensing performance, and their role in overcoming key challenges such as reproducibility, stability, and scalability. Unlike prior reviews that focus on specific materials such as graphene or carbon nanotubes (CNTs), the current review systematically compares graphene, molybdenum disulfide (MoS_2), CNTs, silicon-based Bio-FETs, and emerging hybrid materials.[47] This comparative approach provides a clearer understanding of how different materials influence Bio-FET sensitivity, selectivity, and real-world applicability. In addition to material advancements, the current review explicitly addresses the critical challenges that hinder the commercialization of Bio-FETs. Previous articles, such as the review by Li et al. on the commercialization of CNT-FET biosensors, primarily focus on a single material platform.[48] In comparison, the current review extends this discussion to all major material platforms and highlights strategies for improving device reproducibility, fabrication consistency, and long-term operational stability. It discusses surface functionalization, passivation layers, and scalable manufacturing techniques as potential solutions, ensuring that Bio-FET technology can transition from research labs to real-world applications. Moreover, it bridges the gap between research innovations and practical applications by exploring the translational potential of Bio-FETs in diverse fields beyond conventional biomedical diagnostics, including point-of-care testings, organ-on-chip systems, and wearable biosensing platforms.[49–51]

A key aspect that sets the current review apart is its integration of Bio-FETs with emerging technologies such as AI-driven biosensing, machine learning for real-time signal processing, and the development of flexible and stretchable Bio-FETs for wearable electronics.[6,52,53] While most existing literature remains focused on static Bio-FET platforms, this review explores the future of intelligent, adaptive, and miniaturized Bio-FET sensors, which are poised to play a critical role in next-generation biomedical and environmental monitoring systems.[54] Finally, the review looks ahead to the future of Bio-FETs by discussing standardization efforts, regulatory considerations, and next-generation fabrication approaches that will be essential for widespread adoption. Unlike previous reviews, which primarily summarize past research, our work provides actionable insights into the future trajectory of Bio-FETs, making it a valuable reference for researchers, engineers, and industry professionals working on advancing this technology.

2. Fundamentals of Bio-FET Technology

Bio-FETs improve upon traditional FETs by integrating biological recognition elements and advanced materials, enabling highly precise and efficient biosensing. This sub-section will highlight the fundamentals of FET operation, the importance of biological elements integration, and the use of advanced materials for enhancing biosensor functionality. Understanding these fundamentals reveals the high sensitivity and specificity of Bio-FETs, making them effective even in complex biological environments.

2.1. Basic Principles of FETs

FETs are among the basic elements in an electronics, serving to regulate the flow of current through a semiconductor material. The designer encompasses four major components: 1) Gate: A terminal that modulates the conductivity of the channel. By applying a voltage to the gate, it creates an electric field, which controls current flow through the channel. 2) Source: The terminal through which current enters the FET. 3) Drain: The terminal through which current exits the FET. 4) Channel: The pathway through which current flows; this is made of semiconductor material (like silicon).[5]

The efficiency of FETs, driven by their voltage-controlled current conduction and high input impedance, makes them ideal electronic components.[55,56] Similarly to other devices, Bio-FETs have been able to carry on the fundamental electrical properties while incorporating extra design modifications for compatibility with biomolecular detection. An important factor in helping Bio-FETs achieve their intrinsic electrical characteristics is the electrostatic gating mechanism. In a standard FET, a gate voltage controls the current flow through the channel. Likewise, in a Bio-FET, interactions of the target biomolecule can induce changes in surface charge that modulate conduction through the channel, thereby effectively functioning as a shift in the gate voltage. This provides a voltage-controlled amplification mechanism by which the Bio-FETs are still functionally able to respond to biochemical signals.[46]

In addition to this, Bio-FETs maintain their high input impedance, which is vital for sensitive detection. The use of nanomaterials, including graphene, transition metal dichalcogenides, and silicon nanowires, enhances this property by decreasing leakage currents and boosting the efficiency of signal transduction.[57] These nanomaterials, unlike conventional silicon FETs, have a larger surface-to-volume ratio, allowing for the highest number of biomolecular activity without disrupting the electrical characteristics. Moreover, through the surface functionalization techniques employed here, Bio-FETs maintain their selectivity and responsiveness to specific analytes while guaranteeing electrical stability. Functionalizing the gate surface with biomolecules like antibodies and aptamers enables specific interactions without disrupting transistor operation. Combining this feature with the very sensitive interaction with biomolecules will allow Bio-FETs to provide high sensitivity, fast response, and label-free operation, allowing the underlying core electrical behavior of FETs to remain intact.[43,58]

2.2. Bio-FET Concept, Principle, and Significance

Bio-FETs incorporate the very basic principles of FETs with the aim of detecting biological molecules, thus becoming a powerful tool for real-time, label-free sensing. These devices have biological recognition elements such as DNA, enzymes, or antibodies adsorbed onto the surface of the FET, allowing them to interact with specific biomolecules directly. The main components of a Bio-FET include: Biological Recognition Elements:

These elements selectively bind to target molecules, known as analytes. For instance, DNA strands are able to recognize and bind their corresponding sequences. Enzymes can be utilized to detect metabolic changes in the body, such as glucose levels. In addition, antibodies can be used to detect specific proteins (antigens), which may indicate the presence of disease. Electrical Transduction: Biological interactions (like DNA hybridization or antigen–antibody binding) induce variations in charge distribution in the surrounding vicinity of the FET's surface. These variations are then transduced into electrical signals by changes in channel conductivity, influenced in most cases by pH or ionic concentration.

2.2.1. Structural Composition and Fabrication of Bio-FETs

A Bio-FET is constructed by integrating a biological recognition element with a FET platform, enabling real-time, label-free biomolecular detection. The fundamental structure of a Bio-FET consists of the following key components: 1) Semiconductor Channel: It acts as the conduction pathway between the source and drain electrodes. Traditionally made of silicon, but advanced materials like graphene, transition metal dichalcogenides (TMDs), and silicon nanowires offer enhanced sensitivity and biocompatibility.[59] 2) Gate Dielectric Layer: An insulating layer (e.g., SiO_2, HfO_2) that separates the channel from the gate and prevents leakage currents. In Bio-FETs, the dielectric also serves as a sensing interface, where biomolecular interactions induce an electrostatic potential that modulates the channel conductivity. 3) Source and Drain Electrodes: Provide electrical contacts to the semiconductor channel, allowing for current flow modulation in response to biomolecular interactions. 4) Functionalized Sensing Surface: Biomolecules (e.g., antibodies, DNA probes, aptamers) are immobilized on the gate dielectric or directly on the semiconductor channel. Surface functionalization techniques include self-assembled monolayers (SAMs), covalent bonding, and electrostatic adsorption, which enhance selectivity and specificity for target analytes.[40]

2.2.2. Fabrication and Implementation of Bio-FETs

The fabrication of Bio-FETs involves integrating semiconductor technology with biomolecular recognition elements, enabling highly sensitive and label-free detection of biological analytes. There are two primary fabrication strategies: the Top–Down and Bottom–Up approaches, each with distinct advantages and challenges in achieving high-performance Bio-FETs.[60]

Top–Down Approach: The Top–Down fabrication approach is a lithography-based conventional approach where a bulk material, such as a silicon wafer, is patterned and etched in a systematic manner to produce nanoscale structures. This technique finds widespread use in CMOS-compatible Bio-FETs in conjunction with the requirements of microfabrication such as photolithography, electron beam lithography (EBL), and reactive ion etching (RIE). The key steps in perhaps realization of Bio-FETs according to the top–down approach are 1) substrate preparation: the substrate is typically silicon wafers or any other semiconductor material such as silicon-on-insulator; 2) the deposition of semiconductor layer: thin layers of SiO_2 or high-k dielectrics are deposited through one of the following means: chemical vapor deposition (CVD) or atomic layer deposition (ALD); 3) lithography and etching: the desired transistor structure, including source, drain, and gate electrodes, is defined using either photolithography; and 4) biomolecular functionalization: modifying the transistor channel with biorecognition elements such as enzymes, antibodies, aptamers, DNA probes, among others to provide for selective detection.[61,62]

Bottom–Up Approach: This Bottom–Up approach deals with the Bio-FET's fabrication, starting from the atomic level of construction using the intrinsic self-assembly characteristics of nanomaterials-CNTs, graphene, 2D materials like MoS2, black phosphorus, and quantum dots. This has its inspiration deeply implanted in nanotechnology and molecular assembly techniques. The specific steps involved in the fabrication of Bio-FETs using the Bottom–Up Approach include the following: 1) Nanomaterial Synthesis: Nanomaterials of high purity such as CNTs, graphene, and MoS2 are synthesized using a combination of chemical vapor deposition, hydrothermal synthesis, or exfoliation methods. 2) Self-Assembly and Patterning: The deposition of nanomaterials chemically or electrostatically on the transistor channel in a pre-patterned electrode way. 3) Electrode Formation: Building of the source and drain electrodes using techniques of metal evaporation or printing. 4) Biorecognition Functionalization: The bio-functionalization of nanostructured surfaces using antibodies, aptamers, or enzymes for the selective detection of biomolecules.[63–65]

2.2.3. Operational Regions of FETs and Their Role in Biosensing

Depending on the applied gate–source voltage (V_{GS}) and drain–source voltage (V_{DS}), FETs operate in different regions. The regions determine the transistor's behavior and are key in various applications, including Bio-FETs. The Cutoff Region (OFF State) is when V_{GS} is below threshold voltage (V_{TH}), resulting in no conduction through the transistor and hence no current between the source and drain. In Bio-FETs, this region is invoked for baseline signal measurement to provide a well-defined reference state before biomolecular interactions set in. The linear (Ohmic) region occurs when V_{DS} is much less than $V_{GS} - V_{TH}$. In the Region, the transistor behaves as a variable resistor, whereby the drain current increases linearly with respect to V_{DS}. In the case of Bio-FETs, this region is helpful in tuning sensitivities because minor surface charge changes due to biomolecule binding translate proportionately to changes in the drain current. This variable resistance or transition region lies between the Linear and the saturation regions, and here, the transistor transits from resistive mode to saturation. Some biosensing applications exploit this region to realize adaptive response modulation, optimizing detection sensitivity based on analyte concentration. Finally, there is the Saturation Region (Active Mode), when V_{DS} exceeds $V_{GS} - V_{TH}$; hence, full conduction occurs, whereby drain current becomes V_{DS}-independent. This region finds a lot of exploitation in high-sensitivity biosensors where even minor perturbations in gate potential due to biomolecule binding produce considerable changes in the conductivity of the channel. Graphene-based Bio-FETs often operate in this mode due to their remarkable sensitivity to charge variations which render them highly effective for the detection of biomolecular interactions.[66,67]

The significance of Bio-FETs is underscored by their transformative potential for real-time, high-sensitivity detection without requiring molecular labeling. This reduces complexity and cost, making them invaluable for applications in personalized medicine, environmental monitoring, and rapid diagnostics. In glucose monitoring, enzyme-functionalized Bio-FETs (ENFETs) utilize glucose oxidase to catalyze reactions, changing the local pH and producing measurable signals. Similarly, DNA-FETs designed to detect specific sequences, like cancer biomarkers, have shown exceptional utility in point-of-care testing.[28] Bio-FETs offer numerous advantages: 1) Label-Free Sensing: Unlike traditional methods that rely on fluorescent or radioactive tags, Bio-FETs detect interactions directly, eliminating additional preparation steps. 2) Real-Time Detection: The instantaneous signal readouts make them ideal for the dynamic monitoring of biological processes. 3) High Sensitivity: Advanced materials like graphene and silicon nanowires allow for femtomolar sensitivity, enabling the detection of even trace biomolecular concentrations.[68] For instance, in diabetic patients, ENFETs were used for non-invasive monitoring of glucose and provided real-time data through wearable devices. DNA-FETs have shown that they are useful for mutation detection in cancer biomarkers,[69] such as KRAS or BRCA1,[70] which allow early diagnosis and treatment planning. Further applications include the utilization of aptamer-based Bio-FETs for the detection of environmental toxins such as aflatoxins, thus ensuring food safety.[71] Advanced materials such as graphene, silicon nanowires, and carbon nanotubes have greatly enhanced the performance of Bio-FETs by improving their sensitivity, specificity, and stability in complex biological environments. Besides, new methods of fabrication have been developed, like 3D printing and soft lithography, allowing Bio-FETs to be scalable for commercialization.[72,73] Recent innovations, including flexible electronics and IoT-enabled Bio-FETs, have expanded their applications into wearable healthcare devices and remote diagnostics. Coupled with artificial intelligence (AI), these devices now have the capability for predictive analytics, allowing early interventions in critical conditions. Whether used in disease monitoring, environmental assessments, or personalized healthcare, Bio-FETs are shaping the future of multidisciplinary applications, offering both researchers and industry professionals a transformative technology with vast potential.[39]

2.3. Types of Bio-FETs

The functionalization of Bio-FETs transforms basic transistors into highly specific biosensors capable of detecting minute biological signals. This section outlines the various strategies used to immobilize biomolecular probes, including aptamers, antibodies, and enzymes, onto the transistor's surface. Readers will gain insights into how these strategies optimize sensitivity, specificity, and stability for real-world biosensing applications.

2.3.1. Deoxyribonucleic Acid Field-Effect Transistors (DNA-FETs)

DNA-based FETs (DNA-FETs) integrate single-stranded DNA (ssDNA) probes onto the surface of a FET, enabling highly specific and label-free detection of target DNA sequences. When complementary DNA strands hybridize, the resulting surface charge variation modifies the local electric field at the gate, inducing a measurable change in the conductivity of the semiconductor channel. This electronic transduction mechanism eliminates the need for molecular labeling, allowing real-time, highly sensitive biosensing applications in molecular diagnostics, environmental monitoring, and personalized medicine. The versatility of DNA-FETs has propelled their use in a variety of fields, from early cancer biomarker detection to the development of DNA-based data storage technologies, bridging biosensing with computational applications.[13,74] The performance of DNA-FETs has been significantly enhanced through the integration of microfluidic platforms and CMOS technology. These advancements have increased sensitivity, improved automation, and enabled noninvasive diagnostics. For example, microfluidic DNA-FETs have demonstrated the ability to detect cancer-associated microRNAs at attomolar levels, with detection limits reaching 84 aM for microRNA-195 and 75 aM for microRNA-126 within a rapid 5-h workflow. Such developments pave the way for miniaturized, high-throughput point-of-care diagnostic devices, particularly for early-stage breast cancer detection (**Figure 1A**).[75] In addition to microfluidic integration, the use of advanced 2D materials such as molybdenum disulfide (MoS_2) and graphene has driven further improvements in DNA-FET performance. MoS_2-based DNA-FETs, functionalized with DNA tetrahedrons, have exhibited outstanding detection limits of 1 femtogram per milliliter (fg mL^{-1}) for prostate-specific antigen (PSA), a crucial biomarker for prostate cancer diagnosis (Figure 1B).[76] Meanwhile, graphene-functionalized DNA-FETs have demonstrated exceptional sensitivity, detecting vascular endothelial growth factor (VEGF165), a key biomarker for cancer and vascular diseases, at concentrations as low as 3.24 picograms per milliliter (pg mL^{-1}, Figure 1C).[77] The high conductivity and large surface area of graphene provide enhanced sensitivity, making it an essential material for next-generation biosensing platforms. Beyond traditional biomedical applications, DNA-FETs are expanding into nontraditional fields such as DNA-based data storage.

Selective DNA hybridization mechanisms enable ultrasensitive, reusable nanoporous DNA-FETs, achieving sub-femtomolar detection limits while offering a stable platform for computational functionalities (Figure 1D).[78] Additionally, the integration of Cu^{2+}-DNA/MoS_2 hybrid structures has opened new avenues in cancer drug interaction monitoring. These hybrid DNA-FETs exhibit remarkable reusability and a sensitivity of 1.7×10^3 A/A, making them ideal for real-time doxorubicin detection, a widely used chemotherapy drug (Figure 1E).[79] Such advances in hybrid material-based biosensors enhance both sensitivity and specificity, enabling real-time drug response monitoring in oncology and precision medicine. The rapid evolution of DNA-FETs into multifunctional biosensing platforms highlights their growing importance in biomedical diagnostics, drug development, and emerging nanotechnology applications. However, challenges such as long-term stability, device reproducibility, and large-scale manufacturability remain key barriers to commercial adoption. Addressing these challenges through the standardization of fabrication techniques, surface passivation strategies, and hybrid material integration will be essential for ensuring the reliability and scalability of DNA-FETs. Future re-

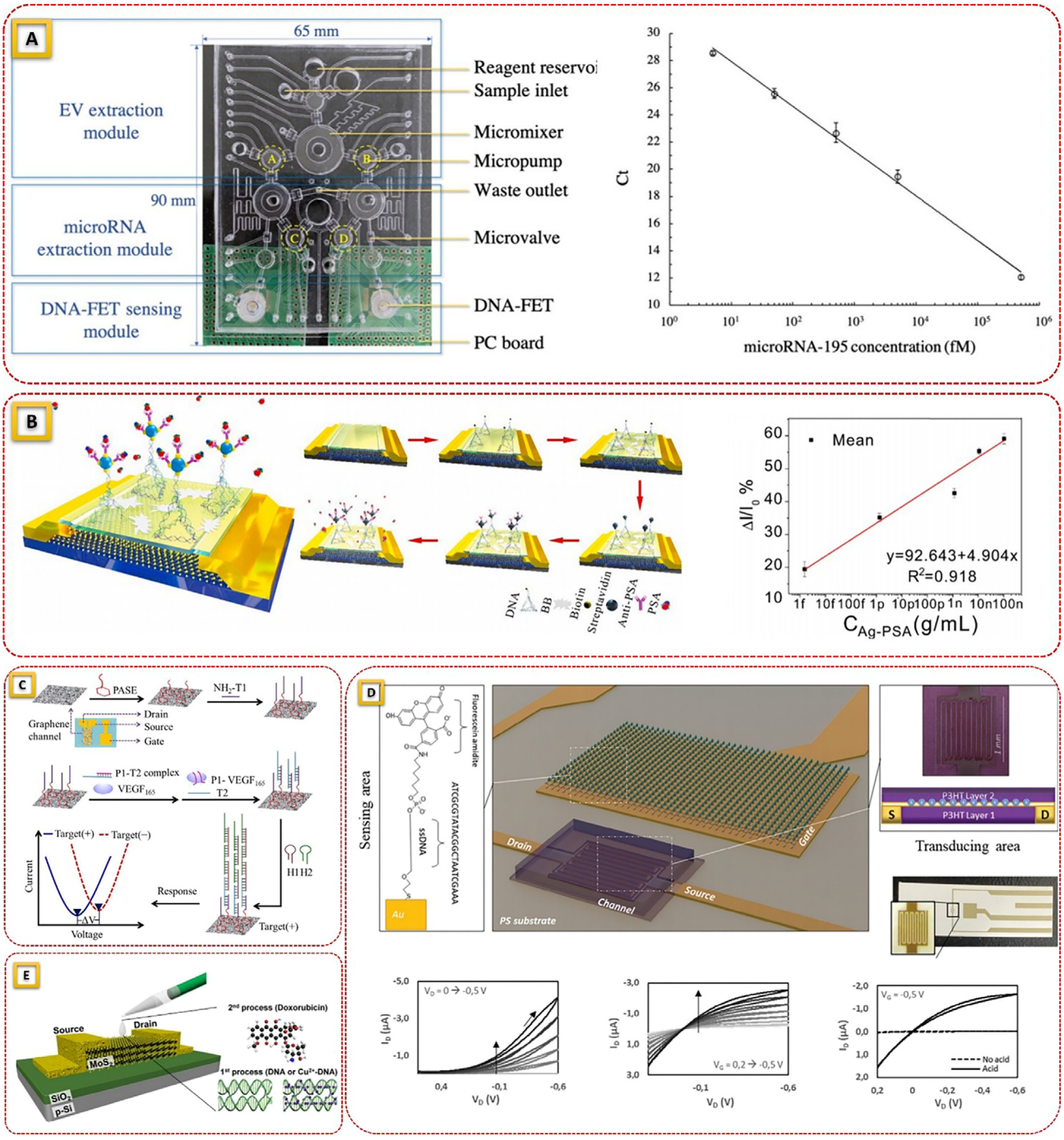


Figure 1. A) Microfluidic-based DNA-FET systems to detect microRNAs, reproduced from[75] with the permission of Springer. B) DNA-based functionalization of 2D MoS_2 FET biosensor for ultrasensitive detection of PSA, reproduced from,[76] copyright Elsevier. C) Graphene DNA-FETs for VEGF Detection, reproduced from[77] copyright Elsevier. D) Nano-porous DNA Field Effect Transistor with Potential for Random-Access Memory Applications, reproduced from[78] Copyright Wiley. E) M-DNA/Transition Metal Dichalcogenide Hybrid Structure based Bio-FET, reproduced from,[79] Copyright Science Report.

search must focus on enhancing device robustness while maintaining ultrahigh sensitivity, enabling DNA-FETs to transition from research labs to real-world clinical and industrial applications. To further illustrate the diversity of applications, materials, and innovations in this field, the following comparative

Table 1 summarizes key features and outcomes of notable DNA-FET studies. This provides a comprehensive overview for researchers and practitioners alike, highlighting the progress and opportunities in leveraging DNA-FETs for real-world applications.

Table 1. Various case studies summary regarding DNA-FETs.

Ref.	Target biomolecule	Materials and techniques	Detection limit	Applications	Significance
[75]	microRNA-195 and microRNA-126	CMOS technology with microfluidics	84 aM for microRNA-195, 75 aM for microRNA-126	Early-stage breast cancer diagnosis	Automated, sensitive platform for early cancer diagnosis
[78]	Single-stranded DNA for data storage	Nanoporous DNA probes	Sub-femtomolar	DNA-based data storage	Bridges biosensing and computational functionalities
[79]	Doxorubicin	Cu^{2+}-DNA/MoS_2 hybrid structure	1.7×10^3 A/A	Real-time monitoring of cancer drug interactions	High reusability and sensitivity for oncology applications
[76]	Prostate-specific antigen (PSA)	MoS_2 functionalized with DNA tetrahedrons	1 fg mL^{-1}	Cancer biomarker detection	Advances in 2D materials for biosensing
[77]	Vascular endothelial growth factor (VEGF165)	DNA-functionalized graphene FET	3.24 pg mL^{-1}	Cancer diagnostics and vascular health monitoring	Scalable and versatile diagnostic tool
[80]	RNA	Graphene FET (G-FET) with PNA and DNA probes	0.1 aM for PNA probe, 100 aM for DNA probe	RNA detection in biomedical research and early clinical diagnosis	High specificity and rapid detection of RNA
[81]	Various biomolecules (e.g., DNA, RNA)	InGaZnO field-effect transistors (IGZO FETs)	0.1 pM	Low-cost detection of biomolecules	Cost-effective and highly sensitive biosensing

2.3.2. Enzyme-FETs (ENFETs)

Enzyme-based FETs (ENFETs) combine the high sensitivity of FET technology with the specificity of enzyme interactions to detect biomolecules in real time. Their working principle involves the following steps:

1) Enzyme Immobilization: Specific enzymes are immobilized on the FET's sensing surface. These enzymes act as biological recognition elements, selectively interacting with the target analyte (e.g., glucose, urea, acetylcholine).
2) Target Analyte Interaction: When the target molecule interacts with the enzyme, a chemical reaction occurs. For instance, in glucose sensing, glucose oxidase catalyzes the oxidation of glucose to gluconic acid, releasing hydrogen peroxide (H_2O_2).
3) Signal Transduction: The product of the enzymatic reaction (e.g., ions, protons, or chemical by-products) causes a change in the local charge near the FET surface. This alters the electric field at the gate region of the FET.
4) Electrical Signal Generation: The change in the local electric field modulates the conductivity of the FET's channel (e.g., graphene, CNT, or rGO). This results in a measurable electrical signal, such as a shift in the threshold voltage (Dirac point) or changes in current between the source and drain terminals.
5) Signal Amplification and Detection: The amplified electrical signal correlates with the concentration of the target analyte, enabling highly sensitive detection.[4,82,83]

ENFETs have emerged as highly efficient biosensing technologies, providing unique solutions to issues in medical diagnostics, environmental monitoring, and therapeutic research. ENFETs combine enzymes with FET technology to provide highly sensitive, selective, and real-time biomolecule detection. Leveraging advanced materials such as graphene and reduced graphene oxide, these devices achieve improved stability, selectivity, and reproducibility. Key case studies demonstrate their revolutionary potential, highlighting how ENFETs are driving innovations and tackling current challenges across various fields. For instance, a silk fibroin-encapsulated graphene FET was developed for glucose detection (**Figure 2**A), leveraging the biocompatible and flexible nature of silk fibroin for enzyme immobilization. This device demonstrated a linear detection range of 0.1–10 mM and a detection limit (LOD) of 0.1 mM, showcasing its potential for wearable and implantable continuous glucose monitoring.[84] Similarly, a silk fibroin hydrogel-encapsulated graphene FET improved enzyme stability and minimized nonspecific adsorption, achieving an impressive LOD of 200 nM with excellent regenerative capabilities over multiple cycles (Figure 2B).[85]

Reduced graphene oxide-based enzyme FETs (rGO-EnFETs) have shown significant potential in neurological research, particularly in studying acetylcholine (ACh) for Alzheimer's disease. These devices quantified ACh levels within a range of 1 µM–10 mM and assessed enzyme-inhibitor interactions (Figure 2C), making them valuable tools for drug screening and therapeutic research.[86] Similarly, an rGO-based FET functionalized with urease demonstrated the ability to detect urea concentrations as low as 1 µM while simultaneously quantifying heavy metals like Cu^{2+} at 10 nM (Figure 2D). These examples demonstrate the multifunctionality of ENFETs in advancing both medical diagnostics and environmental monitoring.[87] In the realm of lactate monitoring, a graphene-based lactate biosensor demonstrated high selectivity and stability over 12 days, indicating its suitability for critical care diagnostics, as shown in Figure 2E. This device underscores the importance of ENFETs in point-of-care applications, particularly for conditions like ischemia and respiratory failure.[88] Additionally, a dual-gated CNT-based enzyme FET (shown in Figure 2F) demonstrated enhanced sensitivity for acetylcholine detection, highlighting its utility in neurological diagnostics and therapeutic studies.[89]

In addition to their impressive advancements in biosensing, ENFETs have also benefited from the integration of emerging technologies such as machine learning.[90] Machine learning

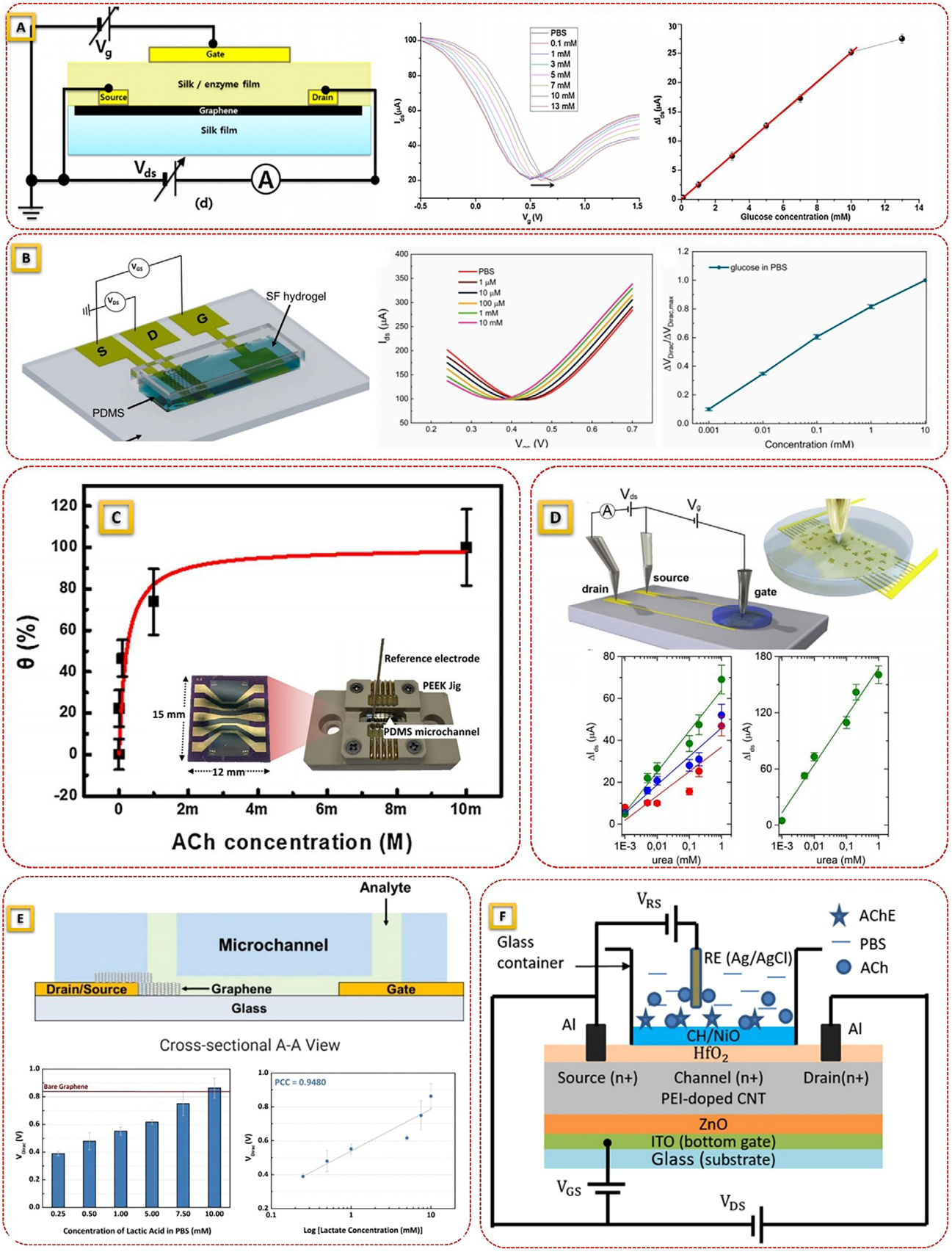


Figure 2. A) Silk fibroin-encapsulated graphene FET for glucose detection, reproduced from,[84] copyright Elsevier. B) Silk fibroin hydrogel-encapsulated graphene FET for glucose detection, reproduced from,[85] copyright Elsevier. C) Reduced graphene oxide-based enzyme FETs for acetylcholine (ACh) for Alzheimer's disease detection, reproduced from,[86] copyright Elsevier. D) Reduced graphene oxide-based enzyme FETs for urea detection, reproduced from,[87] Copyright Elsevier. E) A graphene-based enzymatic biosensor using a FET for L-Lactic Acid Detection, reproduced from,[88] Copyright MDPI. F) Carbon nanotube-based dual-gated enzyme FET for acetylcholine detection, reproduced from,[89] Copyright Springer.

algorithms have been employed to optimize sensor designs, improve detection accuracy, and enable rapid data analysis, making them powerful tools in the evolution of next-generation biosensors. In a recent study, researchers employed a computer model to verify the functions of two biosensors: one that detects lactate and one that detects troponin (cardiac protein). The model was designed based on how electric charges traversed through the sensor, and the model prediction results were in good agreement with lab results. To enhance device performance, a random forest machine learning model was applied to optimize the sensor using a novel figure of merit. The sensitivity and limit of detection (LOD) were subsequently calculated, revealing that polyaniline exhibited superior sensitivity 220 $(nM)^{-1}$ for lactate biosensing and 484 $(g\ mL^{-1})^{-1}$ for troponin detection. Additionally, polyaniline demonstrated nearly ten times lower power consumption due to its exceptionally low threshold voltage of −170 mV, making it an attractive candidate for energy-efficient biosensor applications.[91] This integration of machine learning with biosensor development exemplifies a transformative shift in the field, enabling the creation of highly sensitive, selective, and efficient diagnostic tools. By leveraging computational models and advanced data analytics, researchers are pushing the boundaries of biosensor capabilities, paving the way for more precise and scalable healthcare solutions.

Collectively, these advancements reflect overarching trends in ENFET research, including material innovation, enhanced enzyme stability, and expanded application scope. By leveraging biocompatible materials and multifunctional designs, ENFETs are poised to address pressing challenges in healthcare and environmental sustainability. Their importance lies in their ability to combine high sensitivity with miniaturization, paving the way for real-time, portable, and noninvasive diagnostics. However, challenges such as long-term stability, scalability, and cost-effectiveness must be addressed to unlock their full potential for commercial applications. The following comparative **Table 2** summarizes key features and outcomes of notable Enzyme-FET studies.

2.3.3. Immuno-FETs

Immuno-FETs utilize antigen–antibody interactions to achieve highly sensitive and real-time detection of biomolecules. By integrating precise molecular recognition with the ultrasensitive

Table 2. Different case studies comparison for EN-FETs.

Ref.	Target analyte	Materials/techniques	Detection limit	Applications	Impact
[84]	Glucose	Silk fibroin encapsulation on graphene FET	0.1 mM	Continuous glucose monitoring	Biocompatible, flexible, and wearable for medical diagnostics
[85]	Glucose	Silk fibroin hydrogel encapsulation	200 nM	Regenerative glucose sensing	High specificity and reusability for long-term biosensor applications
[86]	Acetylcholine	rGO-based enzymatic FET	1 µM	Alzheimer's biomarker analysis	Enables drug screening and enzymatic kinetics studies
[87]	Urea, Cu^{2+}	Layer-by-layer urease-modified rGO FET	1 µM for urea, 10 nM for Cu^{2+}	Environmental and health monitoring	Multifunctional biosensor for dual analyte detection
[92]	Glucose, UA, cholesterol	PANI/Nafion-graphene bilayer on OECTs	Not specified	Noninvasive biomarker detection	Broad applicability for saliva-based diagnostics
[93]	L-Arginine	Cascading enzymes (arginase and urease) on rGO	10 µM	Real-time metabolic monitoring	Label-free and selective detection for amino acid analysis
[88]	Lactate	Lactate dehydrogenase on graphene	Not specified	Critical care diagnostics	Stable, low-cost platform for point-of-care lactate monitoring
[89]	Acetylcholine	Dual-gated CNT-based enzyme FET	Not specified	Neurological diagnostics	Enhanced sensitivity for neurotransmitter activity detection
[94]	Nitrate	OFET-based biosensor	45 ppb	Water quality monitoring	Low-cost, flexible platform for environmental applications
[95]	Various biomarkers (e.g., glucose, UA)	ISFET integrated with immunoassay	1 pg mL^{-1}	Point-of-care diagnostics	Portable and cost-effective platform for infectious disease monitoring
[96]	Dopamine	Extended-gate OFET with laccase-linked mediator	0.029 ppm	Urinalysis	Highly selective biosensor for dopamine detection in human urine
[97]	APOA1	Magnetic bead-assisted EGFET	12.5 ng mL^{-1}	Protein biomarker detection	High-performance biosensor integrated with microfluidics

electronic properties of FETs, these biosensors offer an efficient, label-free platform for medical diagnostics, environmental monitoring, and industrial applications. Their working mechanism is based on a series of electrochemical events that occur when a target antigen binds to immobilized antibodies on the FET surface. This interaction redistributes surface charges, modulating the electric field near the gate, which, in turn, alters the conductivity of the semiconductor channel. These electrical variations are then amplified and processed, enabling quantitative analysis of biomarker concentration with exceptional specificity. The use of advanced nanomaterials, such as graphene, silicon nanowires (Si-NW), and MXene-graphene hybrids, has significantly improved sensitivity and detection limits, making Immuno-FETs a powerful tool in various fields.[98,99]

A major strength of Immuno-FET technology lies in early disease detection, where conventional methods often suffer from low sensitivity or time-consuming protocols. A graphene-based Immuno-FET, for example, has demonstrated ultrahigh sensitivity in detecting Lyme disease, utilizing single-chain variable fragment (scFv) antibodies with an exceptional detection limit of 2 pg mL^{-1} (**Figure 3A**).[74] This innovation reduces false positives and enhances the reliability of point-of-care diagnostics, offering a major improvement over traditional immunoassays.[100] Beyond infectious disease detection, Immuno-FETs are transforming cancer diagnostics, particularly for ovarian cancer monitoring. A flexible, multiwalled carbon nanotube /reduced graphene oxide hybrid FET-based apta-sensor has been developed for detecting the CA125 antigen, achieving a detection limit of 5×10^{-10} U mL^{-1} (Figure 3B).[101] The wearable, portable nature of this sensor makes it highly adaptable for real-time health monitoring, addressing the growing demand for personalized cancer diagnostics. The incorporation of rGO enhances sensitivity and long-term stability, ensuring reproducible and accurate biomarker quantification in complex biological fluids.

In addition to medical applications, Immuno-FETs are proving vital in environmental monitoring. A graphene FET has been utilized to detect chlorpyrifos, a highly toxic pesticide, achieving a detection limit of 1.8 femtomolar (fM) (Figure 3C).[102] This level of sensitivity is crucial for detecting trace amounts of environmental pollutants, making Immuno-FETs an effective tool for ecological safety assessments. Similarly, the development of MXene-graphene hybrid FETs has revolutionized virology, enabling the rapid detection of influenza and SARS-CoV-2 with a detection limit as low as 1 femtogram per milliliter (fg mL^{-1}) and a reaction time of only 50 ms (Figure 3D).[30] The synergy between MXene's chemical sensitivity and graphene's superior conductivity provides a scalable and robust approach for pandemic preparedness and virus outbreak monitoring. Further expanding their diagnostic potential, Immuno-FETs based on Silicon nanowires (Si-NWs) have been employed for exosome detection, a critical biomarker for various diseases, including cancer. Functionalized with CD63 antibodies, these sensors achieved a detection limit of 2159 particles per milliliter, allowing label-free, real-time biomarker quantification.[31] This advancement highlights the growing role of Immuno-FETs in liquid biopsy applications, facilitating early-stage cancer detection and personalized treatment strategies. The advancements in Immuno-FETs underscore their broad potential across healthcare, environmental monitoring, and industrial biosensing. The integration of highly selective biomolecular probes, advanced nanomaterials, and cutting-edge sensing architectures has positioned these devices as a powerful alternative to conventional diagnostic methods. However, key challenges remain in ensuring long-term stability, reproducibility, and large-scale manufacturability. Future research must focus on enhancing device durability, developing cost-effective fabrication techniques, and optimizing surface functionalization methods to minimize signal drift and biofouling effects. Addressing these limitations will be crucial for the widespread adoption of Immuno-FET technology in clinical and commercial settings. The following **Table 3** demonstrates the broad applicability of Immuno-FETs across diverse domains, underscoring their transformative potential to address critical global challenges.

2.3.4. Ion-Sensitive FETs (ISFETs)

Ion-sensitive FETs (ISFETs) serve as highly adaptable biosensors, capable of detecting specific ions and biomolecules through real-time electrical transduction. Their functionality is based on surface charge modulation, where interactions between target analytes and a functionalized sensing surface induce local charge redistribution. This alteration in charge density modifies the electric field at the gate, subsequently changing the transistor's conductivity. The resulting variations in electrical signals are processed and quantified, enabling highly sensitive, label-free detection of a wide array of analytes. These unique properties allow ISFETs to be widely employed in medical diagnostics, environmental monitoring, and precision agriculture.[54]

One of the most significant applications of ISFET technology in clinical diagnostics is where nanoribbon-based ISFETs (NR-ISFETs) have demonstrated ultrasensitive detection of prostate-specific antigen (PSA) at a detection limit of 10 pM (**Figure 4A**).[109] The ability to operate directly in human plasma underscores the clinical viability of ISFETs, particularly in early cancer detection. Similarly, a complementary CMOS-based ISFET-photodiode platform has been developed to simultaneously detect glucose and cholesterol in serum (Figure 4B), offering a cost-effective, multi-analyte solution for metabolic health monitoring and disease prevention.[110] These innovations exemplify ISFETs' ability to transform personalized healthcare through low-cost, real-time biochemical sensing. Beyond metabolic and cancer diagnostics, ISFETs are making strides in genetic analysis. A peptide nucleic acid (PNA)-functionalized ISFET array has been shown to detect microRNA Let-7b reliably at concentrations as low as 1 nanomolar (nM), highlighting its utility for point-of-care nucleic acid testing (Figure 4C).[111] The integration of dual-gate ISFET configurations with microfluidic channels has further enhanced sensitivity and efficiency in DNA detection, facilitating rapid molecular diagnostics with minimal sample requirements.[112] These advancements position ISFETs as a key technology in personalized medicine, genetic disease screening, and biomarker discovery.

The versatility of ISFETs extends beyond pure healthcare applications, addressing critical health-related environmental challenges. A graphene-based ISFET integrated with a nitrate ion-sensitive membrane has achieved an ultralow detection limit of 0.041 parts per trillion (ppt) (Figure 4D), offering a powerful tool for real-time water quality monitoring.[113] This capabil-

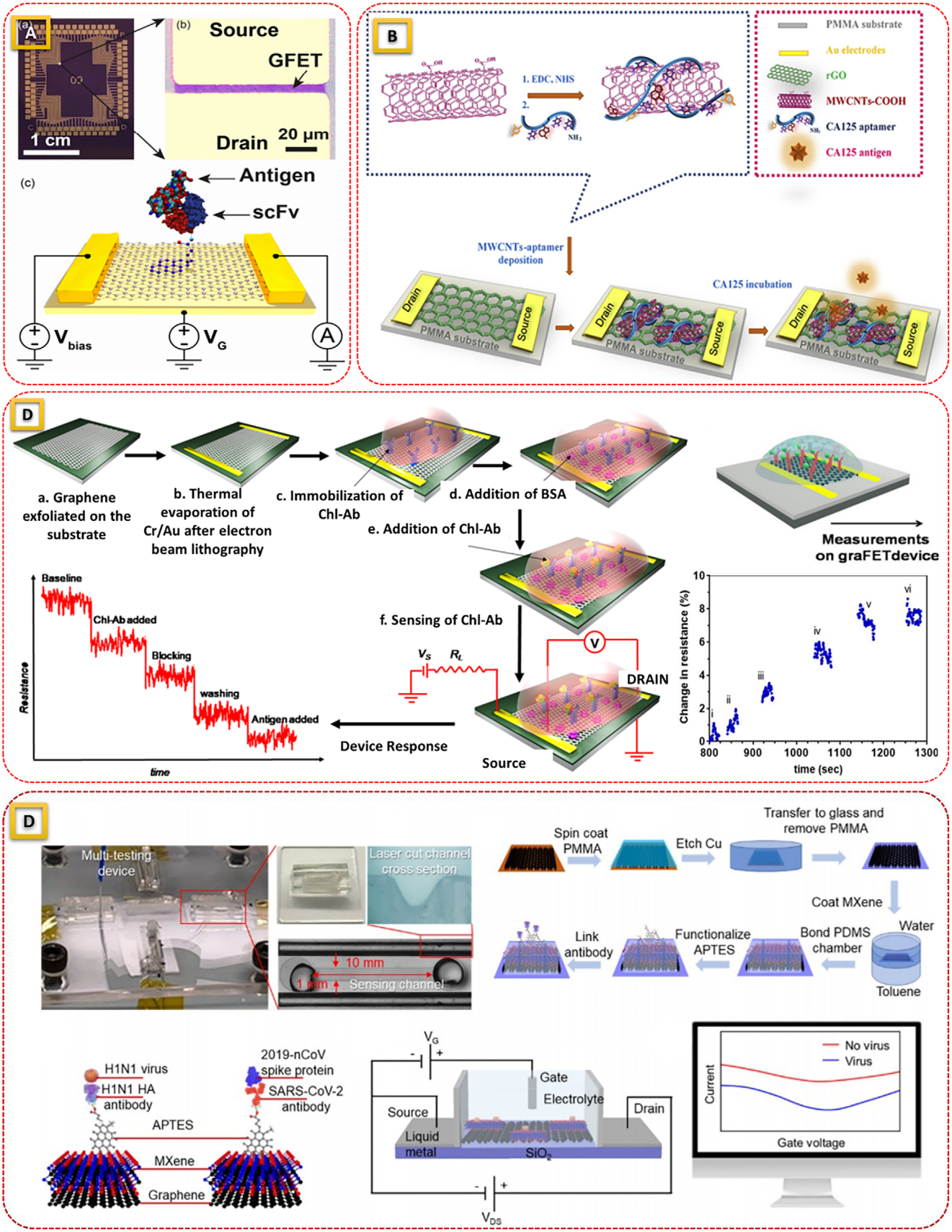


Figure 3. A) Graphene-based Immuno-FETs for detecting Lyme disease, reproduced from,[100] copyright IOP Publishing. B) A flexible, MWCNT-rGO hybrid FET-based aptasensor for CA125 antigen detection, reproduced from,[101] copyright Elsevier. C) Graphene FETs to detect chlorpyrifos, reproduced from,[102] copyright Scientific Reports. D) MXene-graphene hybrid FETs for detecting influenza and SARS-CoV-2, reproduced from,[30] copyright ACS.

ity ensures safe drinking water and contributes to global environmental conservation efforts. Additionally, silicon-on-insulator (SOI)-based ISFETs have been combined with odorant-binding proteins (LUSH) to detect ethanol concentrations as low as 0.001%, underscoring their potential in chemical monitoring and toxic substance detection.[114] These applications highlight ISFETs' role in environmental safety and public health, offering highly precise, field-deployable solutions for contaminant analysis. In agriculture, ISFET-based sensors are driving advancements in precision farming and soil nutrient monitoring. An extended-gate FET (EGFET)-based potassium sensor has demonstrated high sensitivity and stability across a wide concentration range, enabling efficient nutrient management for optimized crop yields (Figure 4E).[115] This innovation reduces fertilizer waste, minimizes environmental impact, and enhances food production sustainability. Furthermore, ISFETs integrated with nitrate detection technologies provide comprehensive soil analysis solutions, ensuring balanced fertilization and resource efficiency.[116] These breakthroughs underscore ISFETs' ability to improve agricultural sustainability while reducing ecological damage, positioning them as crucial tools in modern precision agriculture.

The rapid advancements in ISFET technology illustrate a unifying vision where medical diagnostics, environmental safety, and precision agriculture converge into a single sensing framework. The adoption of graphene, CMOS integration, and dual-gate architectures has significantly enhanced ISFETs' sensitivity, specificity, and real-world applicability. However, challenges such

Table 3. Comparative table of Immuno-FET case studies.

Ref.	Target analyte	Materials/techniques	Detection limit	Applications	Impact
[100]	*Borrelia burgdorferi* antigens	Graphene FET with scFv antibodies	2 pg mL^{-1}	Lyme disease diagnosis	Enhanced early-stage detection and reduced false positives.
[32]	Antibody–antigen complexes	SOI-FET biosensor	Theoretical analysis	Virus detection	Improves design and accuracy in antigen–antibody complex detection.
[33]	Cancer antigens (CEACAM5/1)	Silicon nanowires under EEF	Not specified	Cancer diagnostics	Maximizes antigen–antibody interaction through optimal orientation.
[31]	Exosomes	Si-NW FET with CD63 antibody	2159 particles mL^{-1}	Cancer biomarker detection	Facilitates real-time, label-free exosome analysis for early diagnosis.
[34]	IgG-antigen complexes	DNA origami-based reconfigurable FET	Antigen–triggered	Drug delivery systems	Enables logic-gated, antigen-triggered release of therapeutic payloads.
[103]	Mycobacterium tuberculosis Ag	SWCNT-based FET with Ab85B	0.05 fg mL^{-1}	Tuberculosis diagnostics	Promises point-of-care TB detection with ultralow detection limits.
[104]	Oral cancer biomarker (CYFRA)	WO3 thin-film FET	1.26 pg mL^{-1}	Saliva-based cancer diagnostics	Real-time detection with high specificity and minimal sample volume.
[105]	Japanese Encephalitis Virus (JEV) and Avian Infuenza Virus (AIV)	Graphene FET on Si/SiO_2 substrate	1 fM (JEV), 10 fM (AIV)	Virus detection	Demonstrates scalable, sensitive detection for infectious diseases.
[101]	Ovarian cancer antigen (CA125)	MWCNT/rGO hybrid FET	5×10^{-10} U mL^{-1}	Cancer diagnostics	Portable, wearable platform for personalized health monitoring.
[106]	Streptavidin–biotin reaction	ISFET with microfluidics	Not specified	Protein interaction studies	Enables direct monitoring of antigen–antibody interactions.
[107]	Ebola glycoprotein	rGO dielectric-gated FET	0.001–3.401 mg L^{-1}	Pandemic response	High sensitivity for virus detection via resonance-frequency modulation.
[30]	Influenza and SARS-CoV-2	MXene-graphene hybrid FET	1 fg mL^{-1}	Virus detection	Fast, sensitive, and specific diagnostics for pandemic management.
[102]	Chlorpyrifos	Graphene FET	1.8 fM	Pesticide residue detection	Addresses neurotoxicity concerns in agriculture.
[108]	Human chorionic gonadotropin	Graphene FET with pyrene esters	1 pg mL^{-1}	Pregnancy and cancer diagnostics	Cost-effective, reliable platform for point-of-care applications.

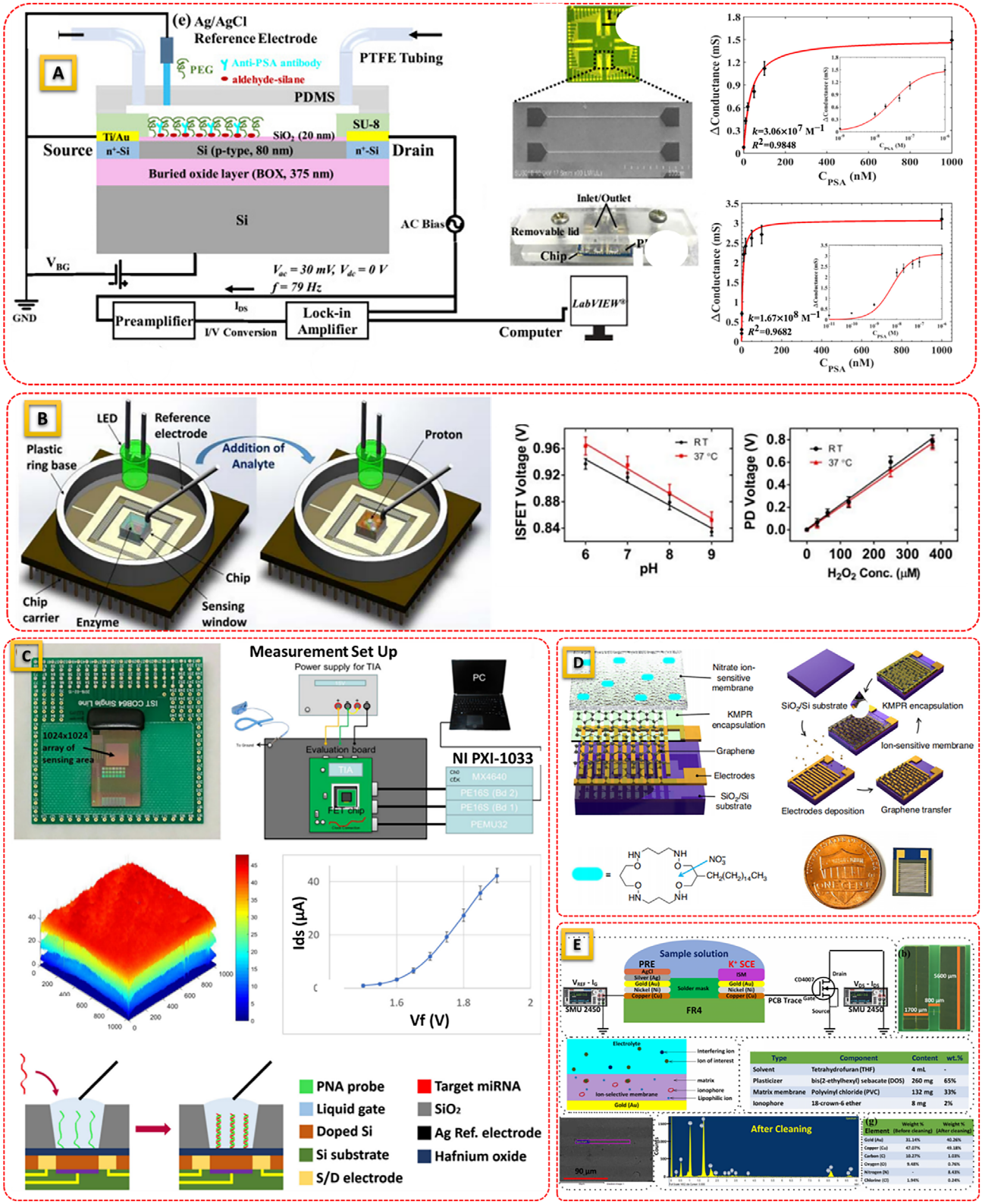


Figure 4. A) A dual-gate nanoribbon-based ISFET label-free detection of prostate-specific antigen, reproduced from,[109] copyright Elsevier. B) CMOS-based ISFET-photodiode platform simultaneously detected glucose and cholesterol in serum, reproduced from,[110] copyright IEEE. C) PNA-functionalized ISFET array for detection of microRNA, reproduced from,[111] copyright Springer. D) Graphene-based ISFET for nitrate detection, reproduced from,[113] copyright Nature. E) ISFET-based sensors address the critical need for efficient nutrient monitoring, reproduced from,[115] copyright IEEE.

Table 4. Comparative table of ISFET case studies.

Ref.	Application	Key features	Detection range	Limit of detection (LOD)	Special remarks
[109]	Protein detection in high ionic strength solution and human plasma	Dual-gate NR-ISFET biosensor with excellent sensitivity and specificity. Detection of PSA in real-time with LOD of 10 pM.	10 pM–1 μM	10 pM	Real-time protein detection for clinical applications.
[117]	pH sensing and DNA amplification	78 × 56 ISFET array with in-pixel quantization. High sensitivity (3.2 μs/pH).	N/A	pH sensitivity of 3.2 μs/pH	Integrated lab-on-chip cartridge for DNA detection.
[118]	KI detection in artificial saliva	Calixarene-based SAM modified ISFET. High selectivity to KI.	≈3×10^{-8} M	≈3×10^{-8} M	Potential for human biological liquid analysis.
[114]	Ethanol detection	LUSH protein fused SOI-ISFET. High sensitivity using dual-gate system.	0.001% – 1%	N/A	Potential for handheld chemical sensors.
[119]	Hydrazine detection	JFET-based ISFET with CuHCF-NPs. High sensitivity and low drift.	1.17×10^{-5}–2.15×10^{-2} M	3.16 μM	Simple and cost-effective hydrazine sensor.
[111]	Nucleic acid detection	PNA-functionalized ISFET array. Robust and reliable detection.	1 nM	1 nM	High-density array for genotyping and DNA detection.
[112]	DNA detection	NR-ISFET with dual-gate mode. Improved sensitivity and specificity.	50 pM	50 pM	Enhanced performance in microchannels.
[120]	pH and protein detection	SnO2 NW-FET with Al2O3 sensitive layer. High stability and sensitivity.	pH 3–10	N/A	Integrates lab-on-chip for automated analysis.
[121]	Proton-based immunoassay (H-ELISA)	Dual-gated ISFET array for high signal throughput.	12.5–125 pg mL^{-1}	12.5 pg mL^{-1}	Compatible with complex biological samples.
[122]	Salmonella detection	ISFET with CeOx gate. Sensitivity to low bacterial counts.	2–3 cells mL^{-1}	2–3 cells mL^{-1}	A reusable sensor with reduced measurement time.
[123]	pH sensing	ISFET with enhanced threshold voltage and low leakage current.	pH 4.67 – 9.3	N/A	Analog study and improved pH sensing.
[116]	Nitrate detection in water	Graphene ISFET with ultralow LOD and wide detection range.	0.1 ppt–100 ppm	0.041 ppt	Record low LOD for environmental monitoring.
[124]	Fabry disease diagnostics (α-galactosidase)	ISFET for enzymatic activity detection. Label-free detection.	10^{-11} M to 3.2×10^{-8} M	10^{-10} M	Optimized for newborn screening.
[125]	CRP detection	ISFET with GPTMS modification. High sensitivity.	0.002–20 μg mL^{-1}	0.002 μg mL^{-1}	Real-time CRP monitoring.
[126]	K^+ ion detection in blood serum	TiO_2-based EGFET. Stable and reproducible performance.	3.5–10 mM	100 μM	Tested in artificial blood serum.
[115]	K^+ ion detection in soil	EGFET with solid-state electrodes. High sensitivity and stability.	10^{-4} to 1 M	10^{-6}	Cost-effective for soil nutrient monitoring.

as long-term stability, signal drift, and mass production scalability remain barriers to widespread commercialization. Future research should focus on improving material robustness, developing antifouling coatings, and optimizing device fabrication techniques to enhance sensor durability and reproducibility. By bridging biochemistry with cutting-edge nanotechnology, ISFETs continue to drive groundbreaking innovations across multiple disciplines. Their seamless adaptability ensures that next-generation biosensors will play a transformative role in addressing some of the most pressing global challenges. The comparative **Table 4** provides a structured overview of ISFET advancements, summarizing their key applications, detection limits, and technological breakthroughs. This serves as a valuable reference for future research, guiding the evolution of ISFET technology toward real-world impact and commercialization.

2.3.5. Aptamer-Based FETs

Aptamer-based FETs (Aptamer-FETs) integrate the high sensitivity of FETs with the specific molecular recognition capabilities of aptamers, offering an advanced biosensing platform for medical, environmental, and industrial applications. Aptamers—short single-stranded DNA or RNA sequences that act as bioreceptors, binding selectively to target molecules such as proteins, small molecules, or ions. Upon binding, the aptamer undergoes a con-

formational change, inducing charge redistribution near the gate of the FET. This variation in charge modulates the conductivity of the transistor channel, generating an electrical signal proportional to the analyte concentration. The amplified and processed signal enables real-time, highly sensitive, and label-free detection, bridging the gap between traditional diagnostics and cutting-edge biosensor technology.[28]

Aptamer-FETs have been extensively explored in biomedical diagnostics, demonstrating ultralow detection limits and high specificity across various disease biomarkers. A crumpled graphene-based FET has achieved highly sensitive detection of dopamine, interleukin-6, and COVID-19 antigens (**Figure 5**A) by optimizing the crumpling ratio to enhance the electric double-layer formation. This advancement addresses critical diagnostic needs in pandemics and chronic diseases, ensuring rapid, scalable biosensing solutions.[127] Further pushing the boundaries of cardiovascular diagnostics, AlGaN/GaN high electron mobility transistor (HEMT) biosensors have enabled label-free detection of cardiac troponin I (cTnI) with exceptional sensitivity and specificity (Figure 5B). This innovation simplifies portable, point-of-care cardiac health monitoring, significantly improving the accessibility of cardiac diagnostics.[128] Expanding this concept, microfluidic aptamer-FET platforms have been developed to enable simultaneous multi-biomarker detection. One such device (Figure 5C) integrates FET sensors functionalized with aptamers for CRP, NT-proBNP, cTnI, and fibrinogen, offering comprehensive cardiovascular health assessments in a miniaturized, portable format.[129]

Beyond cardiovascular diagnostics, graphene-based aptamer-FETs have been employed for metabolic disorder detection, particularly for hormonal imbalances. For instance, a biomimetic graphene aptamer-FET sensor for antidiuretic hormone (ADH) has been designed to mimic kidney receptor functions, providing a breakthrough tool for diagnosing nephrogenic diabetes insipidus.[132] Aptamer-FETs are also proving invaluable in oncology, supporting early cancer detection and precision medicine. Silicon nanowire FETs (SiNW-FETs) functionalized with DNA aptamers have been developed for label-free detection of prostate-specific antigen (PSA), offering high sensitivity and specificity (Figure 5D).[130] This capability highlights the versatility of aptamer-FETs in addressing critical challenges in cancer biomarker detection. Similarly, in neuroscience research, flexible graphene-based FETs functionalized with aptamers have been designed for the simultaneous detection of dopamine and serotonin, ensuring minimal crosstalk and high selectivity (Figure 5E).[131] These advancements provide transformative tools for neurochemical research, supporting mental health diagnostics and pharmacological studies. Beyond neurotransmitter detection, Aptamer-FETs have been instrumental in neurodegenerative disease research. Carbon nanotube-based FETs (CNT-FETs) functionalized with aptamers have demonstrated highly sensitive detection of Alzheimer's biomarkers, such as β-amyloid peptides, in human serum. These sensors outperform traditional techniques, offering a reliable, noninvasive platform for early Alzheimer's diagnosis and large-scale screening.[133]

Beyond medical applications, Aptamer-FETs are expanding into health-related environmental and industrial sectors, demonstrating their versatility in chemical and pollutant monitoring. The advancements in nanomaterial integration, such as graphene, CNTs, and AlGaN/GaN semiconductors, continue to enhance sensor performance, making them scalable and adaptable for diverse applications. However, challenges such as long-term stability, reproducibility, and cost-effective fabrication remain key areas for further research. Future efforts should focus on developing robust immobilization techniques, improving signal amplification strategies, and integrating machine learning for automated data analysis. Aptamer-FETs are emerging as one of the most promising biosensing platforms, capable of bridging molecular biology with advanced electronics. By combining ultra-sensitivity, multiplexed detection capabilities, and real-time analysis, they are poised to redefine diagnostics, environmental safety, and industrial monitoring. The comparative **Table 5** provides a structured summary of key findings, detection limits, and applications, serving as a concise reference for ongoing advancements in Aptamer-FET technology.

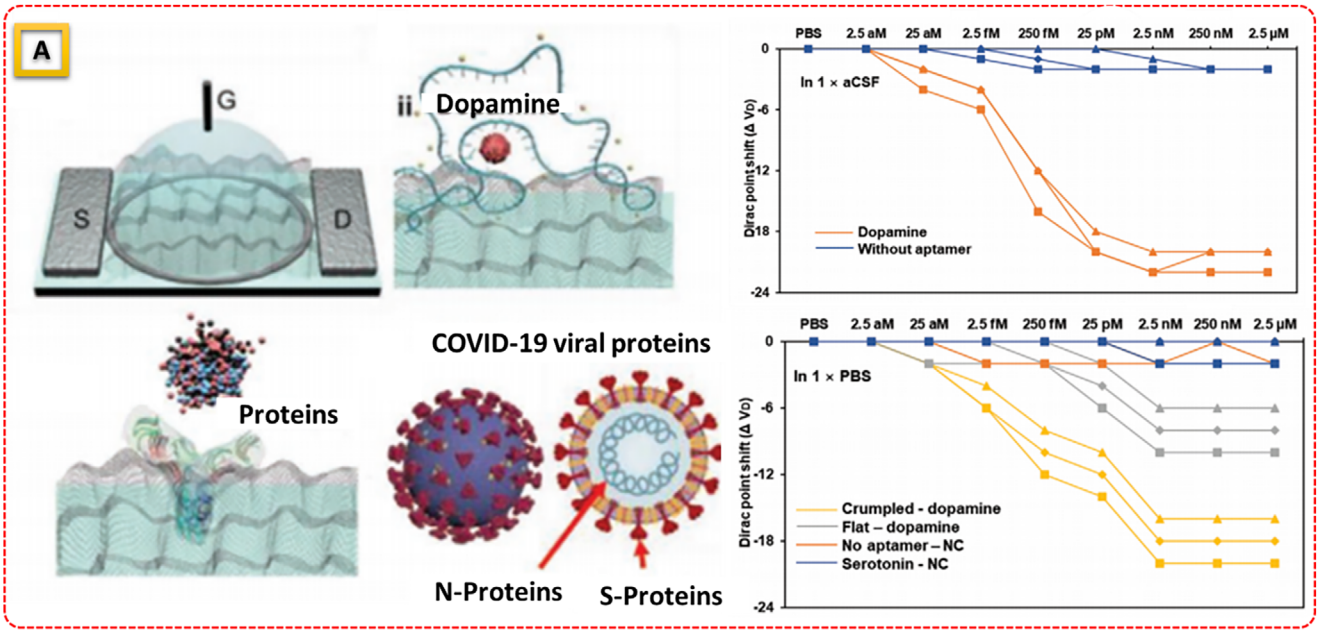
3. Most Reported Materials in Bio-FETs

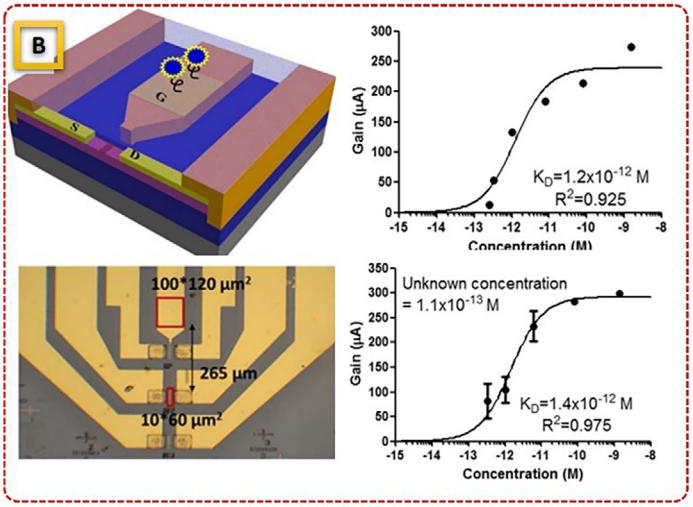
Bio-FETs are versatile due to their capabilities in a range of application areas, particularly when specialist materials and recognition elements have been connected. The use of these devices in the healthcare engagement to biological investigations provides unparalleled sensitivity and selectivity in the detection of a variety of different analytes. This section gives an overview of the main applications of Bio-FETs by advancing in material science and device architecture, showing how these developments enlarged their applications. With a better appreciation of the Bio-FET's practical uses, one can then consider their transformative effects on solving global challenges in health and related sustainability and industry sectors.

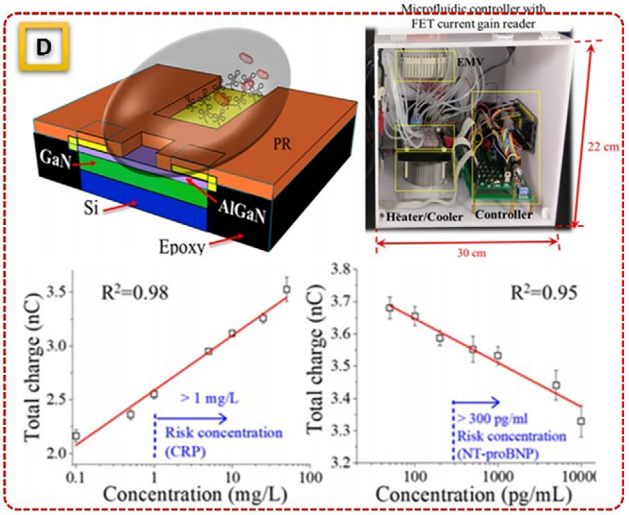
3.1. Laser-Induced Graphene-Based FET

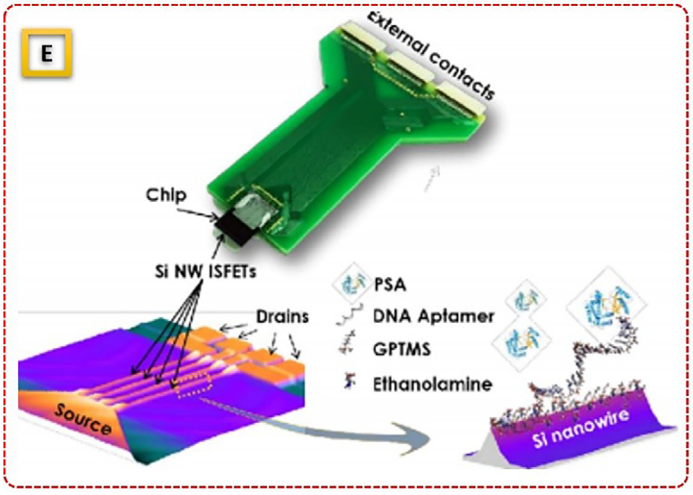
Bio-FETs based on graphene FETs have become a game changer in biosensing, utilizing outstanding characteristics of graphene, including its remarkable conductivity, extensive surface area, flexibility, and biocompatibility. These make graphene an ideal candidate for detecting a variety of biomolecules with superior sensitivity and specificity. The application of graphene Bio-FETs ranges from medical diagnostics, to environmental monitoring and food safety, through to real-time, label-free detection methods which are scalable and workable.[6,49]

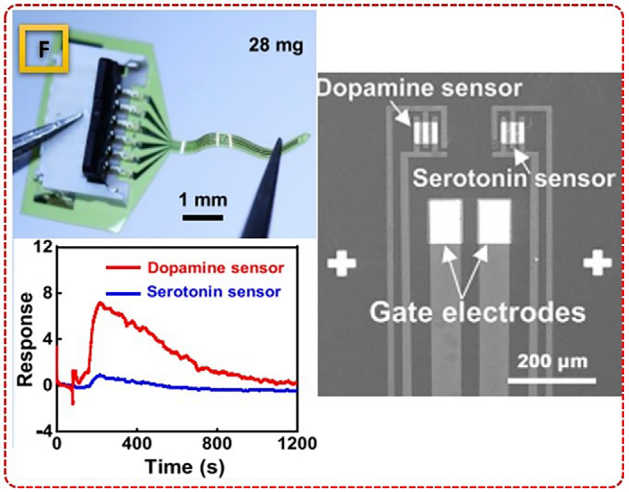
A graphene FET functionalized with pyrene-tagged DNA aptamers demonstrated sensitivity in detecting *E. coli* (**Figure 6**B), addressing critical public health needs and enhancing food safety through rapid and accurate bacterial contamination detection.[144] Guanine-rich aptamers were used to create a graphene Bio-FET for real-time insulin monitoring (Figure 6B), enabling precise insulin dosage prediction and improving diabetes management.[145] Extending its utility to immunology, a graphene monolayer-based FET detected Interferon-gamma (IFN-γ) (Figure 6C), a key biomarker for tuberculosis and immune response.[146] These advancements showcase graphene BioFETs' transformative potential in infectious disease detection, immunological research, and personalized healthcare. Extending beyond healthcare, graphene Bio-FETs also play a pivotal











role in food safety and environmental applications. For example, a covalently bonded graphene FET efficiently detected ochratoxin A (OTA) in spiked wine samples, shown in Figure 6D,[147] showcasing its utility in identifying harmful mycotoxins and ensuring food quality. Similarly, a graphene FET sensor capable of detecting lysozyme, shown in Figure 6E,[148] a vital immune protein, offers a proactive approach to monitoring bacterial infections and chronic conditions. These innovations bridge the gap between real-time biomolecule detection and practical field applications.

Research into neurodegenerative diseases has focused tremendous attention on the integration of graphene BioFETs. Recent developments describe an extended-gate FET (EG-FET) sensor functionalized with LIG intercalated with MnO_2 nanoparticles, aimed at measuring peroxynitrite ($ONOO^-$), an early pathological feature of Alzheimer's disease.[149] This dynamic biosensor has further been fused into a portable and wireless tracking platform for real-time assessment of $ONOO^-$ levels in the brain tissue of AD transgenic mice, enabling a consistent examination of peroxynitrite in the rise of AD before the appearance of massive Aβ plaques. This development highlights the promise that graphene-based BioFETs present for the early detection of neurodegenerative diseases, opening an entirely new diagnostic avenue in Alzheimer's research. In addition, LIG-based BioFETs enable noninvasive detection of chronic diseases, such as early-stage chronic kidney disease, using an EG-FET sensor for urinary Cystatin C (u-Cys C).[150] The graphene EG electrode, modified with gold nanoparticles and chromium on LIG, enhances electrical performance and immobilizes papain for selective Cystatin C detection. This sensor achieves an ultralow detection limit of 0.05 ag μL^{-1} across a broad range (5 ag μL^{-1} to 50 ng μL^{-1}), ensuring high sensitivity. The scalable, label-free platform offers a cost-effective solution for early CKD screening and disease management.

Pushing the boundaries of personalized health monitoring, a wearable graphene BioFET demonstrated highly sensitive detection of cytokines like TNF-α and IFN-γ, as shown in Figure 6F.[151] This device's flexibility and compatibility with biofluids underscore its potential for continuous, noninvasive diagnostics, particularly in inflammatory and autoimmune diseases. The advancements in nucleic acid detection further highlight graphene's transformative role. A graphene-based Bio-FET using engineered DNA probes achieved femtomolar-level sensitivity for DNA hybridization,[152] paving the way for breakthroughs in genetic disease diagnostics and high-throughput screening for personalized medicine. These studies collectively illustrate the versatility of graphene-based Bio-FETs in addressing critical challenges across domains. The seamless integration of graphene's unique properties into real-world applications not only enhances the accuracy and efficiency of biosensing but also opens pathways for cutting-edge nanotechnology. Graphene-based Bio-FETs are poised to redefine diagnostics and next-generation healthcare, environmental safety, and industrial optimization. By bridging molecular biology with monitoring, offering scalable, portable, and highly sensitive solutions for global challenges. **Table 6** provides a structured summary of key findings, detection limits, and applications, serving as a concise reference for ongoing advancements in graphene-based FET.

3.2. Carbon Nanotube FETs

Carbon nanotube FETs (CNT-FETs) have emerged as versatile biosensors, leveraging the exceptional electrical, mechanical, and biocompatible properties of carbon nanotubes.[168] These devices have shown remarkable utility in medical diagnostics and environmental monitoring. During the COVID-19 pandemic, a CNT-FET biosensor detected SARS-CoV-2 S1 antigens in saliva (**Figure 7A**) with an ultralow detection limit of 4.12 fg mL^{-1} and a rapid response time of 2–3 min, offering exceptional scalability for large-scale diagnostics.[169] In cardiovascular health, CNT-FETs have proven effective for detecting C-reactive protein (CRP), a key inflammation biomarker. Notable designs include an immunosensor with a dynamic range of 0.01–1000 µg mL^{-1} for early coronary heart disease detection[170] and an aptamer-based system with a detection limit of 150 pM for portable CRP monitoring in clinical applications (Figure 7B).[171]

CNT-FETs go beyond diagnostic markers to target critical oxidative stress indicators. For instance, a cytochrome c-functionalized CNT-FET enabled real-time detection of hydrogen peroxide (H_2O_2) at femtomolar concentrations, providing vital insights into oxidative damage and related diseases.[172] Similarly, CNT-FET technology has advanced cancer diagnostics through the sensitive detection of exosomal proteins and circulating tumor DNA (ctDNA). A semiconducting CNT FET detected MUC1, a breast cancer biomarker (shown in Figure 7C), at an ultralow limit of 0.34 fg mL^{-1}, distinguishing cancer patients from healthy individuals.[173] Additionally, an all-CNT thin-film transistor integrated with tetrahedral DNA nanostructures (TDNs) achieved a detection limit of 2 fM for circulating tumor DNA (ctDNA) (Figure 7D), enabling multiplexed biomarker detection and advancing oncology diagnostics.[174] Further expanding their utility, CNT-FETs have enabled the detection of inflammatory cytokines such as interleukin-6 (IL-6), a critical marker for cancer and immune responses. Aptamer-functionalized CNT-FET microarrays detected IL-6 at concentrations as low as 1 pg mL^{-1}, which is below the diagnostic threshold for early-stage cancer,[175] (shown in Figure 7E). Similarly, in metabolic health monitoring, a potassium-doped CNT FET demonstrated rapid and selective cholesterol detection with high sensitivity and long-term stability, showcasing its applicability in monitoring metabolic disorders, shown in Figure 7F.[176]

Figure 5. A) Graphene-based FETs optimized with a crumpling ratio to enhance electrical double-layer formation, enabling ultralow detection limits for biomarkers like dopamine, interleukin-6, and COVID-19 antigens, reproduced from[127] with the permission Wiley. B) AlGaN/GaN HEMT biosensor for cardiac troponin I detection, demonstrating label-free and high-specificity diagnostics for point-of-care cardiac health monitoring, reproduced from,[128] Elsevier. C) Microfluidic platform with aptamer-functionalized FET sensors simultaneously detects biomarkers like CRP, NT-proBNP, cTnI, and fibrinogen, reproduced from,[129] copyright Elsevier. D) Silicon nanowire FETs, functionalized with DNA aptamers, for label-free detection of prostate-specific antigen, reproduced from,[130] copyright ACS. E) Flexible graphene-based FETs functionalized with aptamers for real-time monitoring of neurotransmitters such as dopamine and serotonin, supporting neurochemical research and mental health studies,[131] copyright ACS.

Table 5. Comparative table of aptamer-FET case studies.

Ref.	Biomarker/target	Platform	Limit of detection (LoD)	Detection medium	Key features	Special remark
[127]	DNA molecules, small molecules, proteins, COVID-19 proteins	Crumpled graphene FET	Extremely low for COVID-19 proteins	Serum, clinical samples	High sensitivity, detection of viral proteins	Promising platform for point-of-care diagnostics, particularly effective for COVID-19 proteins.
[128]	Cardiac Troponin I	AlGaN/GaN HEMT	0.006–148 ng mL^{-1}	Purified protein solution, serum	Rapid, simplified assay, wide dynamic range	Overcomes charge screening issues, making it ideal for real-time physiological applications.
[134]	Cardiac Troponin T (cTnT)	Au-Co3O4 NR FET	0.1 mg mL^{-1}	Buffer solutions	Synergistic use of Au-Co3O4 NRs	Innovative use of Au-Co3O4 NRs improves sensitivity; requires further exploration for clinical validation.
[129]	CRP, NT-proBNP, cTnI, fibrinogen	Integrated microfluidic FET	Varies for biomarkers (e.g., cTnI: 1–10 000 pg mL^{-1})	Clinical samples	Multi-marker detection, low sample volume	Demonstrates multiplexing capability, crucial for comprehensive cardiovascular risk assessment.
[132]	ADH (Anti-Diuretic Hormone)	Graphene-based GFET	3.55 ag mL^{-1}	PBS, human serum	Ultrasensitive, mimics biological receptors	Mimics natural biological processes, setting a new benchmark for hormone sensing.
[130]	Prostate-specific antigen (PSA)	SiNW-ISFET	1 pg mL^{-1}	Buffer solutions	Multiplexing, low LoD	Achieves multiplexed detection with significant sensitivity; potential for cancer biomarker studies.
[131]	Serotonin and Dopamine	Graphene FET (G-FET)	10 pM	CSF, brain tissue	Flexible, neural probe, multiplexing	Ideal for neurochemical studies due to minimal crosstalk and high sensitivity.
[133]	β-amyloid peptides (Aβ40 and Aβ42)	CNT FET	Sub-femtomolar	Human serum	Mass production, reproducibility	Mass production capability and reproducibility make it viable for large-scale AD screenings.
[135]	Viral nucleic acids	Floating-gate FET	0.13 copies μL^{-1}	Clinical samples	High accuracy, simple functionalization	Novel functionalization approach simplifies sensor preparation; useful for clinical viral RNA detection.
[136]	Rabbit IgG	SiNW-FET	1 pg mL^{-1}	High-ionic strength buffer	Enhanced sensitivity with aptamer	Aptamer-enhanced design improves detection in challenging high-ionic-strength conditions.
[137]	Lysozyme and Thrombin	CMOS-compatible FET	12.0 nM (Lysozyme), 6.7 nM (Thrombin)	Buffer, FBS-spiked solutions	Robust signals, compatible with CMOS tech	Demonstrates CMOS compatibility, paving the way for scalable sensor production.
[138]	Cortisol	OEGFET	27.3 pM	Synthetic buffer solutions	Low-cost, specific to cortisol	Effective for cortisol detection in real-world conditions; a low-cost design adds to its practicality.
[139]	Water contamination indicator (geosmin)	Graphene FET	0.01 nM	Water samples	Real-time monitoring, no special equipment	Real-time, selective water monitoring makes it a valuable environmental sensor.
[140]	Glycated Albumin (GA)	EGFET	0.1–10 µM	Human serum	Dual aptamer sensors, no pretreatment needed	Streamlines diabetes monitoring with no sample pretreatment, ideal for home-use applications.

(*Continued*)

Table 5. (Continued)

Ref.	Biomarker/target	Platform	Limit of detection (LoD)	Detection medium	Key features	Special remark
[141]	Copper ions (Cu(II))	SSA-GFET	10 nM	Fish samples	High recovery rate in fish samples	Significant application in food safety; high recovery rates ensure reliability.
[142]	Ochratoxin A (OTA)	CNT FET	0.2 fM	Food samples	Rapid, selective for OTA	Ultrasensitive detection makes it a potential standard for mycotoxin surveillance in food safety.
[143]	Cardiac Troponin I (cTnI)	SiNW-FET	Ultra-low, optimized	Bio-samples	Mathematical model proposed, signal amplification	Introduces a mathematical model, which can guide future FET biosensor optimizations.

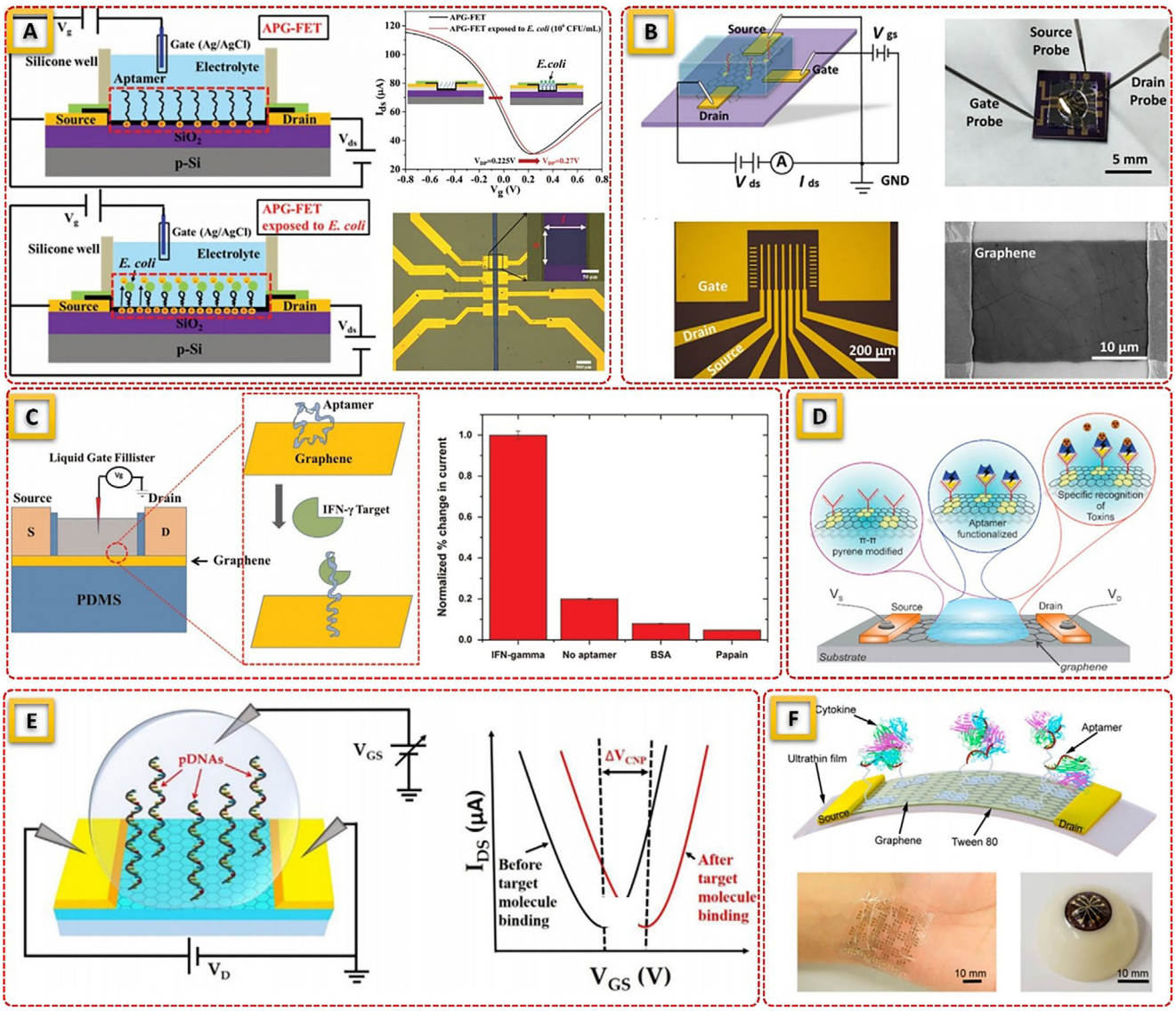


Figure 6. A) Graphene FET functionalized with pyrene-tagged DNA aptamers to detect *E. coli*, reproduced from,[144] copyright Wiley. B) Graphene BioFET for real-time insulin monitoring, reproduced from,[145] Copyright ACS. C) Graphene monolayer-based FET was designed to detect Interferon-gamma (IFN-γ), reproduced from,[146] Copyright Elsevier. D) Graphene FET efficiently detected ochratoxin A (OTA) in spiked wine samples, reproduced from,[147] Copyright MDPI. E) Graphene FET sensor for detecting lysozyme, reproduced from Copyright Frontiers. F) Wearable graphene BioFET for detection of TNF-α and IFN-γ, reproduced from,[151] Copyright MDPI.

Table 6. Comparative table of graphene-based FET case studies.

Ref.	Importance of material	Overarching trends	Key parameters	Applications
[144]	High sensitivity for bacterial detection	High sensitivity, bacterial pathogens	LoD: Low; Target: E. coli	Public health, food safety
[145]	Stable, real-time monitoring for insulin levels	Real-time endocrine biomarker detection	LoD: 35 pM; Target: Insulin	Diabetes management
[146]	Efficient immune biomarker detection	Immune system biomarker applications	LoD: 83 pM; Target: IFN-γ	Infectious disease research
[153]	Attomolar-level detection for anthrax toxin	Pathogen detection for biosecurity	LoD: 1.2 aM; Target: Anthrax toxin	Biosecurity
[154]	Controlled linker density for sensitivity enhancement	Optimization of material sensitivity	LoD: 618 fM; Target: IL-6	Precision diagnostics
[148]	Selective lysozyme detection for infection monitoring	Health monitoring applications	LoD: 10 nM; Target: Lysozyme	Immune system health
[147]	Multiplex toxin detection capability	Multiplexing toxins for broad safety analysis	Multiplex; Targets: Multiple toxins	Toxin multiplexing
[151]	Wearable for real-time cytokine monitoring	Noninvasive wearable diagnostics	LoD: 2.75 pM; Target: Cytokines	Personalized health monitoring
[155]	Enhanced on/off ratio for single-cell detection	Cancer biomarker single-cell sensitivity	LoD: Single-cell; Target: HER2 receptor	Cancer research
[156]	Integrated microfluidics for thrombin detection	Continuous monitoring capabilities	LoD: 2.6 pM; Target: Thrombin	Thrombosis detection
[157]	Simplified aptamer immobilization for IL-6 detection	Device integrity enhancement	LoD: 12 pM; Target: IL-6	Inflammation monitoring
[158]	Label-free CA1 detection for early diagnostics	Simplified clinical diagnostics	LoD: 10 pg mL^{-1}; Target: CA1	Disease biomarkers
[159]	Portable saliva-based cytokine detection	On-the-go health monitoring	LoD: 12 pM; Target: IL-6	Noninvasive diagnostics
[152]	Hybridization chain reaction for ultrasensitive DNA detection	Genetic diagnostics advancement	LoD: sub-fM; Target: DNA	Genetic testing
[160]	Innovative DNA interaction analysis on graphene	Fundamental material interaction studies	LoD: Sub-mismatch detection; Target: DNA	Material interaction research
[161]	Reliable DNA hybridization detection with LEG	Cost-effective sensor production	LoD: 10 fM; Target: DNA	Cost-effective production
[162]	Selective detection with Hall effect measurements	Advanced material interaction analytics	LoD: Specific; Target: DNA	Advanced DNA analytics
[163]	High-throughput DNA screening	Clinical research acceleration	LoD: 10 pM; Target: DNA	Drug and disease research
[164]	CVD-fabricated G-FET for high sensitivity	Elimination of transfer-induced defects	LoD: 100 fM; Target: DNA	Direct fabrication benefits
[165]	Scalable fabrication for DNA hybridization	High-yield, scalable diagnostics	LoD: 1 fM; Target: DNA	Scalable clinical tools
[166]	AuNP-decorated G-FET for clinical DNA testing	Enhanced biomolecular testing	LoD: 1 nM; Target: DNA	Enhanced genetic testing
[80]	Ultrasensitive RNA detection using PNA probes	Broad RNA quantification applications	LoD: 0.1 aM; Target: RNA	Early RNA-based diagnostics
[167]	Deformed graphene for ultrahigh sensitivity	Millimeter-scale ultrasensitive designs	LoD: 600 zM; Target: DNA	Ultrasensitive clinical sensors

Recent advancements in CNT-FET biosensors have been driven by the integration of machine learning (ML) and the Internet of Things (IoT), which have significantly enhanced their analytical capabilities, real-time data processing, and remote health monitoring. One significant study explored the use of ML algorithms to identify critical sensing descriptors in molecular interactions with metal nanoparticle-decorated CNT-FETs. These sensors, based on single-walled carbon nanotubes (SWCNTs), provide highly sensitive molecular detection. By integrating supervised ML techniques with experimental sensor data, the study successfully discriminated among five purine compounds (adenine, guanine, xanthine, uric acid, and caffeine). Using recursive feature elimination and linear discriminant analysis, researchers identified three key parameters transconductance, threshold voltage, and minimum conductance as the most crucial features for analyte classification. The ML models achieved 95% classification accuracy using Linear Discriminant Analysis and 93.4% using Support Vector Machines. These findings highlight the

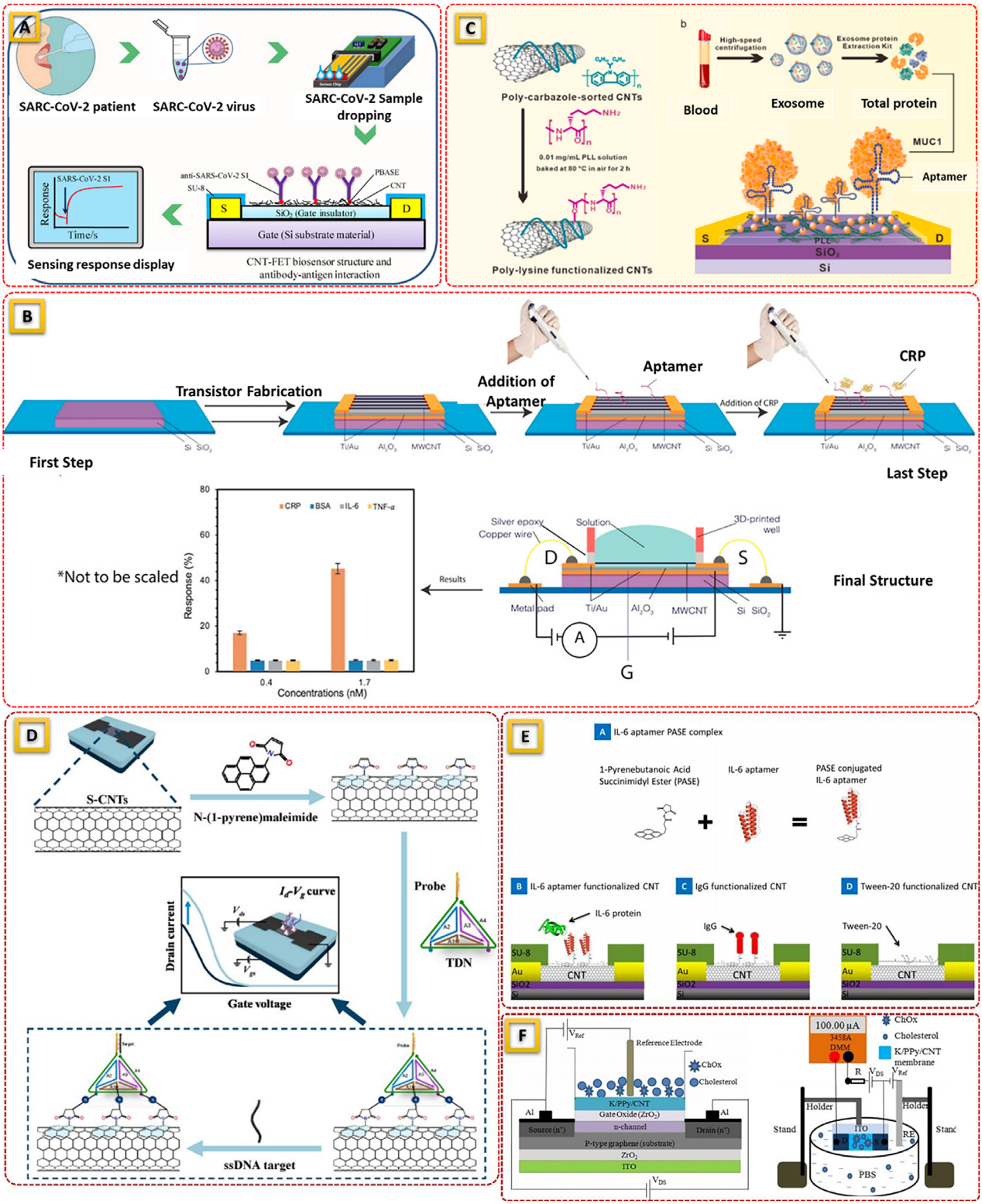


Figure 7. A) CNT-FET biosensor for SARS-CoV-2 S1 antigen detection in saliva, showcasing rapid and label-free COVID-19 diagnostics,[169] copyright Elsevier. (BCNT-FET-based CRP biosensor for clinical inflammation monitoring, highlighting real-world medical applications, reproduced from,[171] copyright ACS. C) Functionalized CNT-FET biosensor for high-sensitivity exosomal protein detection, aiding early cancer diagnosis, reproduced from,[173] copyright Elsevier. D) CNT-based thin-film transistor integrated with tetrahedral DNA nanostructures for multiplexed circulating tumor DNA detection, crucial for oncology diagnostics, reproduced from,[174] copyright Elsevier. E) Aptamer-functionalized CNT-FET microarrays to detect IL-6, reproduced from,[175] copyright MDPI. F) CNT FET for rapid and selective cholesterol detection, reproduced from,[176] copyright Springer.

Table 7. Various CNT-FET case studies showcasing the importance of biomaterial and their applications.

Ref.	Importance of material	Overarching trends	Key parameters	Applications
[169]	Rapid detection of SARS-CoV-2 antigens in saliva	High sensitivity in infectious disease diagnostics	LoD: 4.12 fg mL^{-1}; Fast response (2–3 min)	Pandemic diagnostics and public health
[170]	Broad dynamic range for CRP detection	Wide applicability in inflammation and cardiovascular diagnostics	LoD: 0.01 µg mL^{-1}; Range: 0.01–1000 µg mL^{-1}	Early detection of coronary heart disease
[171]	Portable and reproducible CRP detection	Improved portability for point-of-care testing	LoD: 150 pM; Stable for 14 days	Inflammation and clinical biomarker monitoring
[172]	Real-time detection of hydrogen peroxide (H_2O_2)	Oxidative stress and metabolic disorder research	LoD: 9.13 fM; Response time: ≈1 s	Oxidative stress and cell metabolism studies
[173]	Ultrasensitive detection of breast cancer exosomal protein (MUC1)	Cancer biomarker detection with high specificity	LoD: 0.34 fg mL^{-1}; High specificity	Early cancer detection via exosomal biomarkers
[179]	Label-free detection of ctDNA with tetrahedral DNA nanostructures	Advanced cancer genetics and biomarker multiplexing	LoD: 2 fM; Broad linear range	Genetic cancer diagnostics and precision medicine
[174]	Sensitive detection of IL-6 for early cancer diagnostics	Cytokine profiling for cancer and immune system studies	LoD: 1 pg mL^{-1}; Specific IL-6 detection	Early-stage cancer and immune system diagnostics
[180]	Prostate-specific antigen detection with aligned CNTs	Oncology diagnostics using advanced CNT alignment	LoD: 84 pM; Real-time PSA detection	Prostate cancer diagnostics and protein monitoring
[175]	Rapid and specific detection of IL-6 using CNT microarrays	Multiplexed cytokine detection for immune monitoring	LoD: 1 pg mL^{-1}; Below diagnostic gray zone for cancer	Multiplexed immune and cancer biomarker profiling
[175]	High-sensitivity cholesterol detection using K-doped CNTs	Metabolic health monitoring with rapid response	LoD: ≈1.4 mM; Response time: ≈1 s	Cholesterol monitoring for metabolic health
[176]	Ultrasensitive and scalable detection using FG-CNT FETs	Scalable and universal platform for biomarker detection	LoD: 60 aM; High uniformity over large wafers	Ultrasensitive detection of DNA and microvesicles
[181]	Highly specific detection of Cathepsin E with peptide aptamers	Near-patient testing for cancer diagnostics	LoD: 2.3 pM in PBS; High selectivity	Cancer diagnostics with near-patient applicability
[182]	Multiplexed detection with biomimetic SWCNT films	Broad applicability in biosensors and biofuel cells	Broad dynamic range with multiplexed biosensing	Broad biosensing for environmental and medical use

potential of combining nanomaterial-based sensors with computational models for enhanced precision, selectivity, and real-time analytics.[177] In parallel, IoT integration has expanded the functionality of CNT-FET biosensors for real-time, wireless health monitoring.

A recent study introduced a stretchable, skin-conformal microneedle extended-gate CNT-FET biosensor for continuous sodium monitoring in interstitial fluids, offering minimally invasive health monitoring.[178] The microneedle-based CNT-FET exhibits high sensitivity, a low detection limit, excellent biocompatibility, and mechanical stability for on-body sodium-sensing applications. Moreover, the integration of this device with a wireless data transmitter and IoT cloud enables real-time sodium monitoring and long-term health trend analysis, paving the way for advanced digital healthcare and accurate clinical decision-making. This platform exemplifies how IoT-powered wearable biosensors can revolutionize remote patient monitoring and personalized medicine by providing continuous, real-time biochemical insights.[178] These findings highlight the potential of combining nanomaterial-based sensors with computational models for enhanced molecular detection. By leveraging machine learning-driven approaches, CNT-FET-based biosensors can achieve greater precision, improved selectivity, and robust real-time analytics. This integration is paving the way for next-generation biosensing technologies, advancing applications in healthcare, environmental monitoring, and biomedical research.

To summarize the insights and advancements from the various CNT-FET case studies, the following **Table 7** provides a structured comparison. It highlights the importance of materials, overarching trends, key parameters, and diverse applications of CNT-FET biosensors. This comprehensive overview bridges the detailed explanations provided earlier and presents the case studies in a format that allows for easy comparison and evaluation of their transformative potential in medical, environmental, and industrial applications. Below, the table outlines these case studies, showcasing the versatility and adaptability of CNT-FET technology across different domains.

3.3. Reduced Graphene based FETs

Reduced graphene oxide-based FETs (RGO-FETs) is another powerful tool for biosensing in medical diagnostics and environmental monitoring. An RGO-FET functionalized with single-stranded DNA probes enabled real-time detection of lysozyme, an immune protein, with a detection range of 10 nM to 1 µM (**Figure 8A**), offering early warning for bacterial infections.[148] In biodefense, an aptamer-functionalized RGO-FET detected the

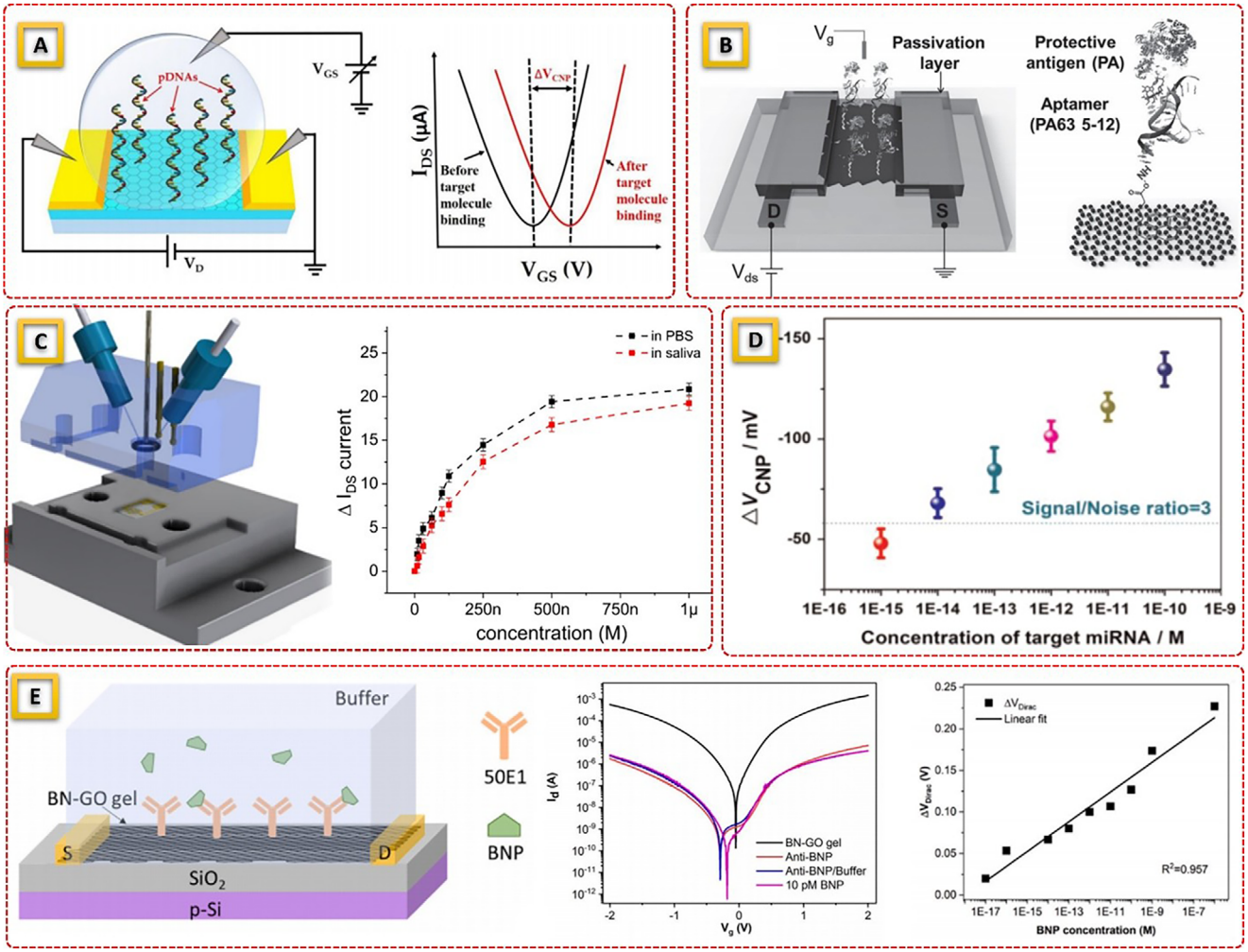


Figure 8. A) RGO-FET functionalized with single-stranded DNA probes enabled for lysozyme-specific immune protein detection, reproduced from,[148] copyright Frontiers. B) RGO-FET for detection of the anthrax protective antigen, reproduced from,[153] copyright Wiley. C) RGO-FET functionalized with RNA aptamers for selective detection of HPV-16 E7 protein, reproduced from,[183] copyright Springer. D) RGO-FETs utilized peptide nucleic acid (PNA) probes to detect microRNAs, reproduced from,[184] copyright Elsevier. E) Boron and nitrogen co-doped graphene oxide FET for detecting B-type natriuretic peptide, reproduced from,[185] copyright Elsevier.

anthrax protective antigen (PA) with ultra-sensitivity, achieving an unprecedented LOD of 1.2 aM through gold nanoparticle signal amplification (Figure 8B).[153] In a similar manner, an RGO-FET functionalized with RNA aptamers selectively detected HPV-16 E7 protein in saliva at an LOD of 100 pg mL^{-1}, demonstrating potential for noninvasive cervical cancer diagnostics (Figure 8C).[183] RGO-FETs have shown remarkable advancements in biomarker detection. For instance, a PNA-functionalized RGO-FET detected microRNAs with an LOD of 10 fM, enabling precise sequence differentiation (Figure 8D).[184] Furthermore, an RGO-FET with CD63 antibodies quantified exosomes at 33 particles μL^{-1}, effectively distinguishing prostate cancer patients from healthy individuals.[186] Another RGO-FET achieved femtomolar sensitivity for PSA detection across six orders of magnitude.[187] Expanding to cardiovascular diagnostics, a nitrogen co-doped graphene oxide (BN-GO) FET BN-GO FET detected B-type natriuretic peptide at an exceptional LOD of 10 aM, with a dynamic range spanning 11 orders of magnitude (Figure 8E).[185] These innovations highlight the transformative potential of RGO-FETs in medical diagnostics. Collectively, these studies highlight the versatility and sensitivity of RGO-FETs across various applications, from early cancer detection and heart failure diagnostics to pathogen monitoring and biodefense. Their ability to operate label-free in complex biological environments, coupled with rapid response times and scalability, establishes RGO-FETs as a cornerstone in advancing biosensing technologies.To consolidate the insights from the detailed case studies on RGO-FET biosensors, the following **Table 8** provides a comparative overview. It highlights the importance of materials, overarching trends, key parameters, and applications across diverse domains. This structured comparison bridges the descriptive narratives and presents the studies in a clear format for easier evaluation and understanding of their transformative potential. Below, the table outlines these findings and emphasizes the versatility of RGO-FET technology.

Table 8. Comprehensive comparative table of all RGO-FET case studies.

Ref.	Importance of material	Overarching trends	Key parameters	Applications
[148]	Real-time monitoring of lysozyme for infection prevention	Immune system and bacterial infection monitoring	10 nM–1 µ detection range	Early infection warning and immune system monitoring
[153]	Ultrasensitive detection of anthrax protective antigen (PA)	Pathogen detection for biodefense	LoD: 1.2 aM; AuNP signal amplification	Biodefense and pathogen detection
[183]	Selective detection of HPV-16 E7 protein in saliva samples	Noninvasive diagnostics for HPV	LoD: 100 pg mL^{-1}; RNA aptamer functionalization	HPV diagnostics and cervical cancer screening
[188]	Detection of DNA through PNA-DNA hybridization	Sensitive detection of genetic biomarkers	LoD: 100 fM; PNA hybridization specificity	Genetic and disease biomarker diagnostics
[189]	Dual-aptamer detection of cancerous microvesicles (HepG2-MVs)	Cancer biomarker detection with high specificity	LoD: 84 particles μL^{-1}; Broad linear range	Early-stage cancer biomarker profiling
[184]	Detection of miRNA for early cancer diagnostics	Gene-related disease diagnostics	LoD: 10 fM; Specific miRNA detection	Cancer diagnostics using genetic biomarkers
[187]	Ultrasensitive detection of PSA complexes for prostate cancer	Prostate cancer biomarker detection	LoD: Femto level; Dynamic range over 6 orders	Early prostate cancer detection
[190]	Detection of *E. coli* in water with a single-cell sensitivity	Pathogen detection in environmental samples	Single-cell detection in 50 s	Environmental pathogen detection
[185]	Exosome detection for cancer diagnostics	Cancer diagnostics using exosome quantification	LoD: 33 particles μL^{-1}; Serum sample validation	Cancer exosome quantification for diagnostics
[191]	Ultrasensitive glucose detection in biological fluids	Metabolic disorder diagnostics	LoD: 1 nM; Rapid response within 1 s	Metabolic health monitoring
[101]	Flexible sensor for ovarian cancer antigen CA125	Cancer biomarker detection in flexible devices	LoD: 5.0 × 10^10 U mL^{-1}; Flexible device integration	Portable ovarian cancer diagnostics
[192]	Quantification of low-concentration cancer exosomes	Label-free cancer diagnostics	Label-free exosome detection	Cancer biomarker and exosome quantification
[184]	Electrical stability for miRNA detection in biological fluids	Stable miRNA detection in complex environments	Electrical and solution stability for miRNA detection	Reliable miRNA monitoring in clinical samples

3.4. Molybdenum Disulfide (MoS_2)-Based FETs

Molybdenum disulfide (MoS_2), a 2D material from the transition metal dichalcogenide (TMDC) family, has emerged as a powerful platform for FET biosensors due to its exceptional electronic properties, high surface-to-volume ratio, and chemical stability. MoS_2-based FETs offer ultrasensitive, label-free detection capabilities and versatility across various applications, from healthcare diagnostics to environmental monitoring. Recent advances have demonstrated its potential in detecting a range of analytes with remarkable sensitivity and specificity.

One notable application of MoS_2-based FETs is in antibiotic detection, as demonstrated by a sensor designed for kanamycin determination.[193] Using a hybrid aptamer structure shaped by complementary DNA strands, this sensor achieved high selectivity for kanamycin over structurally similar antibiotics, as shown in **Figure 9A**. With a detection limit of 0.66 nM, this work highlighted MoS_2's ability to address challenges in antibiotic detection through innovative probe engineering. Expanding this concept to hormone monitoring, a nanomesh MoS_2-based FET was developed for cortisol detection.[194] By introducing nanoscale holes in the MoS_2 channel to increase active binding sites, the sensor achieved a 10^9-fold enhancement in sensitivity compared to pristine MoS_2-based FETs. This advancement facilitated cortisol detection in complex biological matrices like serum and saliva (shown in Figure 9B), underscoring the material's versatility in stress-related diagnostics. The sensitivity of MoS_2-based FETs extends to genetic and prenatal testing. A few-layer MoS_2-based FET was employed for label-free DNA hybridization detection of the hybridization of DNA molecules (shown in Figure 9C,[195] leveraging electrostatic gating effects to achieve a detection limit of 10 fM and a dynamic range of 10^6. Building on this capability, a monolayer MoS_2-based FET functionalized with gold nanoparticles demonstrated its efficacy in noninvasive prenatal testing for Down syndrome.[196] This sensor reliably detected chromosome-specific DNA fragments at concentrations below 100 aM, paving the way for early and reliable prenatal diagnostics, shown in Figure 9D. A CRP biosensor utilizing Au nanoparticle-decorated MoS_2 nanosheets achieved an exceptional detection limit of 8.38 fg mL^{-1}, highlighting its potential for compact diagnostic devices.[160] In bladder cancer diagnostics, MoS_2-based FET sensor arrays demonstrated multi-target detection by identifying biomarkers like NMP22 and CK8 in urine at detection limits as low as 0.027 aM, showcasing its capability for comprehensive cancer screening.[161]

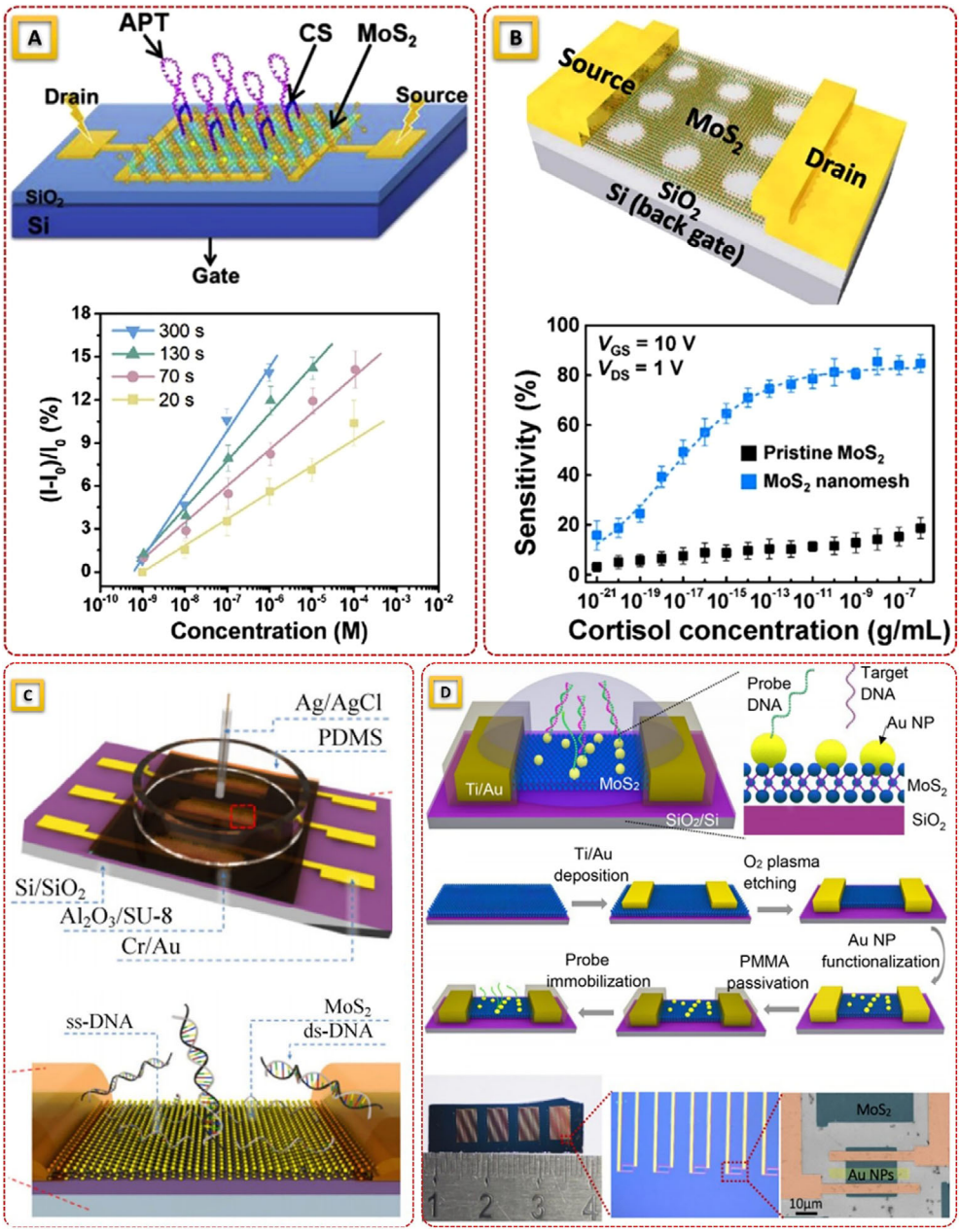


Figure 9. A) MoS_2-based FETs a sensor designed for kanamycin determination, reproduced from,[193] with the permission of Elsevier. B) MoS_2 FET for cortisol detection, reproduced from,[194] copyright, Electronics Square. C) MoS_2-based FET for label-free DNA hybridization detection of DNA molecules, reproduced from,[195] copyright Springer. D) MoS_2-based FET functionalized with gold nanoparticles for Down syndrome detection, reproduced from,[196] copyright ACS.

MoS_2 has also advanced wearable technology, exemplified by a smart contact lens integrated with MoS_2-based FETs that monitors glucose levels, corneal temperature, and optical information in real time.[162] Combining high sensitivity, robustness, and biocompatibility, MoS_2 enables next-generation solutions for diagnostics and wearable healthcare. The discussed case studies highlight the versatile applications of MoS_2-based FETs across diverse domains, including healthcare diagnostics, environmental monitoring, and wearable technology. From detecting antibiotics and stress hormones to enabling noninvasive prenatal testing and cancer biomarker identification, MoS_2-based FETs showcase exceptional sensitivity and specificity. Their integration into multifunctional platforms, such as smart contact lenses and scalable device fabrication processes, further exemplifies their transformative potential. To provide a comprehensive overview, **Table 9** summarizes the key aspects of these studies, emphasizing their detection limits, target analytes, and unique features. This organized comparison helps in understanding the advancements and applications of MoS_2-based FET biosensors.

Table 9. Comprehensive comparative table of MoS_2-based FET case studies.

Ref.	Target analyte	Detection limit	Key feature	Application
[193]	Kanamycin	0.66 nM	Selective antibiotic detection with aptamer	Healthcare diagnostics and food safety
[194]	Cortisol	10^9-fold enhancement	Nanomesh for enhanced sensitivity	Stress-related diagnostics
[195]	DNA hybridization	10 fM	Label-free DNA detection	Genetic and molecular diagnostics
[196]	Trisomy 21 DNA fragments	< 100 aM	Prenatal testing for Down syndrome	Noninvasive prenatal testing
[197]	PMO-DNA hybridization	6 fM	PMO-DNA hybridization	Disease diagnostics
[198]	C-reactive protein	8.38 fg mL^{-1}	Integration with CMOS technology	Compact diagnostic devices
[199]	TNF-alpha and Streptavidin	60 fM	Ambipolar response for improved sensitivity	Advanced cancer detection
[200]	Interleukin-1β	1 fM	Cycle-wise quantification of biomolecules	Immunoassay for low-abundance biomolecules
[201]	MoS2 applications overview	N/A	High throughput exfoliation	Scalable device fabrication
[202]	Glucose	300 nM	Rapid glucose detection	Glucose monitoring
[203]	Bladder cancer biomarkers	0.027 aM,м	Simultaneous biomarker detection	Bladder cancer diagnosis
[76]	Prostate-specific antigen	1 fg mL^{-1}	Ultrahigh sensitivity	Prostate cancer diagnostics
[204]	Glucose and temperature	Multiple Analytes	Multifunctional smart lens	Wearable healthcare devices

4. Challenges, Recent Advances, and Future Directions in Bio-FET Development

Bio-FETs are emerging as transformative tools in biosensing, offering high sensitivity and real-time analysis. However, their development faces significant material-level challenges that impede their broader application, particularly in clinical diagnostics. Addressing these challenges is crucial for achieving reliable signal transduction, long-term stability, and scalable fabrication processes.

4.1. Material Reproducibility and Consistency in Fabrication

Material variability forms a great deal of concern when it comes to the reproducibility of Bio-FET signal transduction. Performance in Bio-FETs resides in the materials used, and for this reason, Graphene, MoS_2, and CNTs may all have their own unique challenges leading to discrepancies in device qualities. Graphene has been widely regarded as the material of choice for biosensing applications because of its large electrical conductivity and surface sensitivity. A typical fabrication of graphene may vary in defect density, surface functionalization, and crystallinity and this leads to performance variability between devices. This characterization poses a major concern for fulfilling the reliability requirements to be adopted, especially in clinical applications.[45] Much like MoS_2 and CNTs, uniform electrical and structural properties are challenging here. The materials may tend to be apparently inhomogeneous, resulting in variations of their electronic properties, thereby directly affecting their effectiveness in biosensing applications. With the lack of standardization in the procedures of synthesis, this variability calls for efforts toward procedures that could promote reliable manufacturing standards.[205]

In order to tackle the above-stated disadvantages, researchers are investigating several advanced techniques in synthesis, for example, defect-engineered materials and single-crystal growth methods. Defect-engineered materials have the potential to enhance the electronic characteristics of nanomaterials through highly tunable defect types and densities incorporated during the fabrication of such materials. Furthermore, these methods of single-crystal growth could result in a better quality of materials with uniform properties, which are important for the reliable performance of the sensors.[206] Such advancements in synthesis are imperative for the enhancement of reproducibility and reliability of Bio-FETs, in order that the materials are maintained to the level of the same degree in terms of electronic, mechanical, and chemical properties across different devices. In addition to material synthesis, exact and standardized functionalization protocols are also very important in achieving predictable signal responses in Bio-FET devices. Such covalent bonding and self-assembled monolayers provide for a new and convenient way of immobilizing recognition elements onto the surface of the sensor. Covalent bonding will, in turn, significantly heighten the stability and specificity of biomolecular interactions.[207] Meanwhile, self-assembled monolayers could create a controlled surface chemistry that reduces nonspecific adsorption and enhances the signal transduction capabilities of the sensors.[55,208]

Additionally, the utilization of AI, including ML, is rapidly expanding across all facets of materials science, which includes discovery, synthesis, characterization, and performance. ML is considered a promising tool in materials synthesis and characterization, with expectations for innovative applications in the near future.[209] It has emerged as a revolutionary tool in materials science research, facilitating quick and precise analysis of complex material properties.AI algorithms are capable of identifying the most efficient and automatable pathways for chemical synthesis and can also assist in the identification and optimization of catalysts. Unlike human chemists, AI-driven synthesis ensures consistent, reproducible results across multiple iterations. Researchers are exploring methods to accelerate discovery by integrating automated experiments, AI, and high-performance computing. Generative AI is reshaping material science by reading, writing, hypothesizing, and solving complex problems. An ensemble neural network-based decision-making algorithm enables more efficient material formulation optimization. Incorporating AI-enhanced quality control mechanisms can improve reproducibility, minimize defects, and ensure that Bio-FET devices

maintain consistent performance across large-scale production batches. The successful application of these functionalization strategies is crucial for optimizing the sensor's sensitivity and selectivity, ultimately leading to more reliable and reproducible signals that are essential for clinical diagnostics.[210,211]

4.2. Operational Durability and Long-Term Stability

The long-term stability of Bio-FETs in biological environments poses significant challenges, primarily due to the degradation of materials used in these sensors. Materials such as graphene and other 2D materials are particularly vulnerable to factors like oxidation, moisture, and interactions with complex biological fluids. These interactions can lead to gradual performance degradation, often referred to as performance drift, which ultimately compromises the reliability of the sensors in real-world application.[212] Oxidation and moisture can alter the chemical composition and electronic properties of graphene and 2D materials, adversely affecting their conductivity and sensor response. In addition to environmental degradation, biofouling remains a critical issue, where the nonspecific adsorption of biomolecules onto the sensor's active surface obscures its sensing capabilities. This phenomenon not only introduces noise in the sensor signals but also reduces the specificity of the detection, leading to false or inconsistent readings. Effective strategies to overcome biofouling are essential for enhancing the long-term operational capability of Bio-FETs.[213]

In efforts to combat biofouling, innovative material coatings such as polyethylene glycol (PEG) and zwitterionic polymers have been developed. These coatings have been recognized for their efficacy in preventing nonspecific protein adhesion, thereby maintaining a clearer surface for effective sensing. However, there is a critical trade-off associated with these coatings: while they can significantly reduce fouling, they often compromise the sensor's intrinsic sensitivity and limit the detection capabilities of Bio-FETs when complex biological samples are analyzed.[214,215] To address the dual challenges of material degradation and biofouling, hybrid organic–inorganic interfaces have emerged as a promising solution. The integration of durable inorganic materials, such as titanium dioxide (TiO_2) or silicon dioxide (SiO_2) nanolayers, with the organic sensing layers of Bio-FETs appears effective in enhancing chemical stability. Recent studies demonstrate that these nanolayers can significantly improve the robustness of Bio-FETs against oxidative and moisture-induced degradation while preserving their functional properties.[216] Another critical avenue of research is the development of adaptive self-healing materials. These materials can repair minor defects and structural damage caused by environmental degradation, thereby prolonging the operational lifespan of Bio-FETs. Moreover, the use of superhydrophobic coatings can help prevent moisture absorption and biofouling, further enhancing durability in biological conditions.[217,218]

4.3. Sustainability and Environmental Impact of Bio-FET Materials

The increasing adoption of Bio-FETs raises concerns regarding their environmental impact, including e-waste generation and material recyclability. Addressing sustainability concerns is critical for environmentally responsible development as Bio-FET technology becomes more commercialized.[219]

4.3.1. Recyclability of Bio-FET Materials

Most Bio-FETs rely on advanced nanomaterials such as graphene, MoS_2, silicon nanowires, and CNTs, which have excellent electrical properties but pose challenges for recyclability.[220] Traditional semiconductor materials, such as silicon-based FETs, contribute significantly to e-waste due to their non-biodegradable nature and difficulty in recovering valuable elements from discarded electronic components.[47] However, emerging materials and fabrication strategies are being explored to enhance the recyclability of Bio-FETs. The development of Bio-FETs using biodegradable substrates, such as cellulose-based nanomaterials, silk fibroin, and polylactic acid (PLA), presents a promising avenue for reducing environmental impact.[6,221] These materials can decompose naturally without releasing harmful residues, making them suitable for disposable biosensors in point-of-care diagnostics and environmental monitoring. Recent advancements in transient electronics have enabled the fabrication of dissolvable Bio-FETs, where the entire device can degrade under controlled conditions (e.g., exposure to water or biofluids).[43,222] Materials such as magnesium, zinc oxide, and water-soluble polymers (e.g., polyvinyl alcohol) are being explored to develop fully degradable Bio-FET platforms that minimize long-term e-waste accumulation. Efforts to incorporate conductive and semiconducting materials that can be easily recovered and reused in future devices are gaining attention. For instance, water-based exfoliation techniques for graphene and MoS_2 allow for the efficient recovery of these materials from discarded Bio-FETs, reducing the need for fresh raw material extraction. Additionally, metal nanoparticle-based conductive inks that can be reclaimed and repurposed in printed electronics are being developed.[223]

4.3.2. Minimizing Electronic Waste in Bio-FET Fabrication

Electronic waste generated from discarded biosensors is a major environmental concern, especially as disposable Bio-FET devices become more widely adopted.[224] To mitigate this issue, several strategies are being explored: 1) Sustainable Manufacturing Approaches: Green synthesis methods, such as hydrothermal and solvothermal techniques, are being employed to produce Bio-FET materials with minimal chemical waste. For instance, eco-friendly reduction methods for graphene oxide using plant extracts or other nontoxic reagents eliminate the need for hazardous chemicals like hydrazine. 2) Energy-Efficient Fabrication: Conventional semiconductor fabrication involves high-temperature processes and vacuum-based techniques, which are energy-intensive and environmentally taxing. Alternative approaches, such as solution-based processing, inkjet printing, and roll-to-roll fabrication, significantly reduce the carbon footprint of Bio-FET production while maintaining high performance. 3) Reusable and Modular Bio-FET Designs: Instead of single-use sensors, researchers are exploring modular Bio-FET architectures where the sensing elements (e.g., aptamers, antibodies, or enzymes) can be replaced without discarding the entire device.

This concept not only enhances the longevity of Bio-FET platforms but also minimizes material wastage.[5,6,225]

4.3.3. Sustainability in Next-Generation Bio-FET Applications

As Bio-FETs transition into real-world applications, integrating sustainability considerations into their lifecycle design will be critical. Several future directions can drive environmentally friendly innovation: 1) Circular Economy Approach: Adopting a circular economy model for Bio-FET production, where end-of-life devices are collected, dismantled, and reused, can significantly reduce e-waste. Implementing closed-loop recycling systems within manufacturing facilities will ensure that valuable materials, such as precious metals and nanomaterials, are efficiently recovered and repurposed. 2) Regulatory and Policy Considerations: Governments and regulatory bodies are enforcing stricter guidelines for as waste management, prompting researchers and manufacturers to develop sustainable alternatives. Standardized certification for biodegradable and recyclable Bio-FETs can help promote their adoption in commercial applications. 3) Eco-Friendly Packaging and Disposal Solutions: Beyond the device itself, packaging and disposal methods must also align with sustainability goals. Developing compostable or recyclable packaging for Bio-FET-based sensors, coupled with public awareness campaigns on responsible disposal, can further reduce their environmental footprint.[226,227]

Finally, as Bio-FET technology becomes more widely used there is an increasing concern about its sustainability that needs be addressed. By incorporating biodegradable materials, recyclable components, and energy-efficient manufacturing methods, the next generation of Bio-FETs can offer high-performance biosensing capabilities with minimal environmental impact. Collaboration among researchers, industry stakeholders, and policymakers is will be essential to Bio-FET technology towards sustainable and eco-friendly future.

4.4. Scalability in Fabrication

Bio-FET fabrication's scalability is limited by complex and costly the manufacturing process. For instance, the techniques such as CVD that are used for graphene and liquid-phase exfoliation for MoS_2 are stumbling blocks for any reasonable scaling up.[228] These techniques essentially require highly controlled environmental conditions and specialized equipment for processing, making it very difficult in an economically viable situation for high-production requirements. Issues arise in large part because retaining the structural integrity and the electronic properties of the materials during these fabrication processes becomes highly critical.[229] CVD, for example, can defect the graphene layers if proper monitoring is not employed, while liquid-phase exfoliation, although applicable, simply results in a lower yield of monolayer materials and inconsistency in quality. The transition from lab-scale to commercial-scale fabrication becomes entirely impossible due to all of these problems, therefore limiting the scope of application of Bio-FET technologies to real situations.[230]

With roll-to-roll manufacturing and inkjet printing are emerging as pioneering techniques, showing advancement towards addressing the scalability challenges of conventional approaches. Continuous production of uniform thin films is conducted through roll-to-roll manufacturing; hence, high-throughput manufacturing at a lower price can be achieved. This process holds great potential for working with flexible substrates incorporating solution-based materials.[231] Another promising alternative is inkjet printing, which specifically enables the deposition of materials and patterns in a targeted manner to suit given applications. This technique minimizes waste and gives better control over material properties. Thus it is a viable method for Bio-FET fabrication. Recent developments indicate that integrating inkjet printing may have the capabilities to significantly streamline the manufacturing process of Bio-FET devices and reduce production costs, therefore allowing for greater user accessibility to Bio-FET technologies applicable in biosensing and diagnostics.[232,233]

In addition, it is important to integrate scalable manufacturing methods with CMOS technology to pave the way for the Bio-FETs' mass production. CMOS technology is an industrially established platform for electronic integration in the semiconductor industry.[230,234] Efforts to align the Bio-FET fabrication processes to CMOS-compatible methods are still ongoing. Such synergy would bring along many benefits, such as decreased production costs, improved performance, and some added compatibility with currently existing electronic systems. With the utilization of CMOS technology, Bio-FETs could, therefore, be produced at an attractive price range while ensuring that they could easily integrate with complex electronic devices, such as those utilized in health monitoring and diagnosis applications. This integration further augments the potential for higher functionality and thus sets the path toward advanced biosensing platforms that deliver results in a speedy and reliable manner.[6,235] Future Bio-FET Research and Development will primarily be encapsulated in answering challenges prevalent. The Indicative directions always focus on adoption of Roll – to – roll printing as a scalable manufacturing technique, seamless enablement of advanced data analytics and AI to enable better signal processing, and multiplexed sensors that enable single analyte detection. The customization of Bio-FETs fitting to wearable and implantable applications for the realization of continuous health monitoring would potentially be transforming. Protocols for fabrication and testing further accelerated commercialization. In essence, the future of Bio-FET development simply lies in converging material-level challenges with scalability challenges and leveraging innovative techniques and technologies. **Figure 10** illustrates the primary challenges presently confronting the Bio-FETs and their associated future directions succinctly. These directions pave the way for the transformable applications in biosensing and diagnostics toward efficient, reliable, and scalable solutions.

4.5. Minimizing Interference Effects from Complex Biological Samples

Bio-FETs are notably susceptible to interference from complex biological samples, which poses a major limitation to their application. This interference includes pH fluctuations, ionic strength variations, and nonspecific biomolecule interactions, all of which can impact the accuracy and reliability of Bio-FET

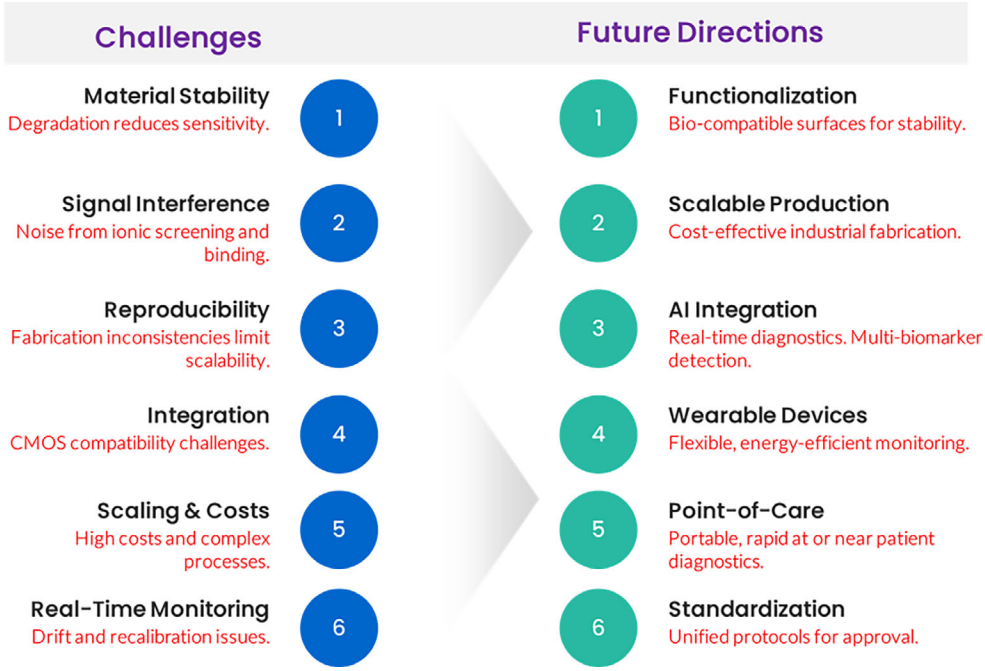


Figure 10. Outlines key challenges and proposed solutions in Bio-FET development, including material-level improvements, scalable fabrication techniques, AI-driven analytics for enhanced signal processing, and integration with wearable and implantable sensors for continuous health monitoring. Each segment highlights potential advancements to improve device stability, reproducibility, and commercialization potential.

measurements.[236] Since Bio-FETs operate by detecting changes in surface charge, they are inherently sensitive to ionic and molecular disturbances present in biological fluids pH shifts can significantly alter the device's response, leading to signal drift and inaccurate measurements. Similarly, the nonspecific adsorption of proteins and other biomolecules introduces unwanted noise, thereby reducing the specificity and selectivity of the Bio-FET. These factors collectively pose substantial limitations to the practical application of Bio-FETs in complex biological environments. To mitigate these interference effects, several strategies can be implemented. Incorporating ion-selective membranes (ISM) helps filter out unwanted ionic noise, ensuring stable sensor response.[237] Additionally, dual-gate Bio-FET configurations with a reference electrode can compensate for pH-induced signal fluctuations, improving measurement accuracy. Surface passivation techniques, such as PEGylation and zwitterionic polymer coatings, prevent nonspecific adsorption, maintaining sensor selectivity in complex biofluids like serum or saliva.[238] This roadmap highlights the integration of advanced material functionalization, scalable production techniques, AI integration, and wearable device compatibility, underscoring the potential of Bio-FETs to modernize healthcare diagnostics. By addressing these challenges and pursuing the future directions outlined, researchers and industry stakeholders can collectively work toward the successful commercialization and adoption of Bio-FET technologies.

5. Summary and Conclusion

Bio-FETs, a special type of biosensors, that combines biology, materials science, and electronics offers efficient solutions to healthcare challenges. Based on advanced materials together with novel functionalization techniques, these devices have raised the bar for sensitivity, specificity, and real-time detection standards. Initially probing cancer diagnosis and monitoring infectious diseases, Bio-FETs propose applications in environmental safety, agriculture, and many more dropped into the challenges facing humanity. Added values in these devices include the interfacing of IoT and flexible electronics, which expand their usefulness in predictive diagnostics and remote healthcare applications. However, long-term stability and reproducibility, along with cutting costs, remain some unsolved questions regarding their year-to-come commercial viability. This review not only captures the remarkable headway made in Bio-FET technology but also sets a stage for interdisciplinary collaboration that may allow the notorious border break in biosensing to follow, leading to a healthier and sustainable future.

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Conflict of Interest

The authors declare no conflict of interest.

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