






Recent Progress in Ion-Sensitive Field Effect Transistor Technology: A Survey of Fabrication Methods and Applications

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ABSTRACT

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Ion-sensitive field-effect transistors (ISFETs) have emerged as a cornerstone technology in modern biosensing, owing to their high sensitivity, label-free operation, and compatibility with complementary metal-oxide-semiconductor (CMOS) manufacturing. This review provides a systematic overview of recent advancements in ISFET fabrication and application, with a focus on the period from 2020 to 2025. The review is organized around four key technological axes: gate material engineering, structural configurations, instrumentation and readout circuits, and biosensing applications. Key findings reveal that the integration of advanced gate materials, particularly two-dimensional (2D) nanomaterials such as graphene and MoS₂, along with nanostructured interfaces, has enabled sensitivity beyond the conventional Nernst limit, while architectural innovations, including dual gate, extended gate, and floating-gate structures, have significantly enhanced modularity, reusability, and electrostatic control. ISFETs have demonstrated broad utility in detecting inorganic ions, nucleic acids, proteins, and microorganisms, underscoring their versatility in clinical diagnostics, environmental monitoring, and wearable technologies. Despite these advancements, persistent challenges such as signal drift, biofouling, and fabrication variability remain. Future directions point toward multi-parametric sensing platforms, artificial intelligence-assisted signal processing, and self-powered systems, positioning ISFETs as foundational components in next-generation precision medicine and point-of-care diagnostics.

1. INTRODUCTION

Ion-sensitive field-effect transistors (ISFETs), which integrate semiconductor technology with chemical and biological detection techniques, signify a substantial advancement in the field of biosensing technology. According to Bergveld's seminal 1970 paper, ISFETs were initially conceptualized as a modified form of the conventional metal-oxide-semiconductor field-effect transistor (MOSFET) [1]. ISFET technology has undergone substantial advancement over the past fifty years. The necessity of labels has been rendered obsolete by the advent of advanced analytical techniques capable of real-time and high-sensitivity identification of ions and biomolecules. The sensors' compatibility with complementary metal-oxide-semiconductor (CMOS) technology and independence from large reference electrodes facilitate their miniaturization and integration into sophisticated analytical platforms [2]. Significant advancements in materials science, particularly in the engineering of gate dielectrics and sensing membranes, have accelerated the development of ISFET-based devices. The list of sensitive layers has expanded to encompass a variety of substances. Some of these substances are well-known materials, such as silicon dioxide (SiO₂) [3] and tantalum oxide (Ta₂O₅) [4]. Other examples of two-

dimensional (2D) nanomaterials include graphene [5] and molybdenum disulfide (MoS₂) [6]. Furthermore, significant advancements in device architecture have led to substantial improvements in the selectivity, sensitivity, and reliability of ISFETs. These include dual-gate [7], extended-gate [8], and floating-gate designs [9].

In recent decades, significant advancements have been made in the field of ISFET devices. The primary factors contributing to this development are their high sensitivity, compact size, cost-effectiveness, and compatibility with semiconductor manufacturing processes. In the early stages of research, the primary focus was on the development of pH sensors, with a particular emphasis on the proton sensitivity of gate materials such as SiO₂ [10] and Si₃N₄ [11]. According to Yates et al. [12], these studies led to the development of the site-junction model and electrical double-layer theory, which explain surface potential changes at the oxide-electrolyte interface. Subsequent advancements have broadened the scope of ISFETs to detect various ions, such as K⁺, Na⁺, and NH₄⁺, by incorporating ion-selective membranes [13]. The advent of innovative materials, including graphene and MoS₂, has precipitated substantial advances in sensitivity and selectivity, thereby enabling responses that exceed conventional Nernst limits [14]. For instance, graphene-based ISFETs have exhibited remarkable performance in detecting multiple ions,

a phenomenon attributed to their high carrier mobility and sensitivity to surface charges [15].

Furthermore, ISFETs have been extensively utilized in biomolecular sensing, encompassing chemicals such as proteins, enzymes, and deoxyribonucleic acid (DNA). The initial application of ISFETs was in the field of DNA sequencing, as pioneered by Janicijevic and Baraban [16]. These researchers leveraged the proton release phenomenon that accompanies nucleotide incorporation, marking a significant advancement in the field. According to the studies cited in reference [17], proteins have also been detected. In these techniques, functionalized gate materials interact with target biomolecules, thereby altering electrical signals. Recent advancements in nanomaterials, including carbon nanotubes (CNTs) [18] and silicon nanowires [19], have led to significant improvements in the sensitivity and specificity of ISFET-based biosensors.

The integration of ISFETs into wearable and healthcare devices represents a significant advance in this field. Sweat and other biofluid indicators can now be monitored in real time by integrating flexible ISFETs with microfluidic systems [20, 21]. These developments highlight the promising potential of ISFETs in disease management and personalized healthcare. Despite these achievements, challenges remain, such as the need to standardize readout topologies, signal drift, and interference [22, 23]. These challenges must be addressed for ISFET to be used in environmental and therapeutic applications.

This review thoroughly evaluates recent advancements in ISFET fabrication and application. The review focuses on fundamental mechanisms, advanced gate materials, structural optimizations, and signal readout methodologies. The review emphasizes the growing use of ISFETs in biosensing applications, including pH monitoring, DNA sequencing, protein detection, and microbial analysis. Lastly, the paper addresses current challenges and proposes future directions for developing flexible, low-power, high-performance ISFET-based biosensors for personalized healthcare, environmental monitoring, and wearable technology. The objective of this review is to provide a comprehensive overview of the most recent advancements in ISFETs for biosensing applications.

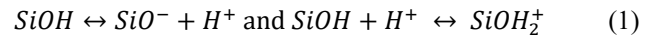
The fundamental principles and sensing mechanisms of ISFETs are delineated in Section 2, thereby establishing the foundation for the ensuing discourse. In Section 3, the most recent advancements in gate materials are examined, with a particular emphasis on various thin films, nanostructures, and two-dimensional materials that have been demonstrated to enhance ISFET performance. In Section 4, a comprehensive evaluation of diverse gate architectures is conducted, encompassing dual-gate, extended-gate, floating-gate, and unmodified-gate CMOS structures. Section 5 presents an overview of key instrumentation and readout circuit techniques for ISFET-based systems, including differential measurement, pH-to-time conversion, ADC architectures, and calibration methods, along with their associated trade-offs. The subsequent section, Section 6, provides an overview of biosensing applications, and Section 7 concludes the study.

2. BASIC SENSING MECHANISMS OF ISFETS

ISFETs are a class of chemically sensitive semiconductor devices that are rooted in the conventional MOSFET. Bergveld's seminal 1970 proposal was a pioneering work in

the field, introducing the use of ISFETs for the detection of Na^+ . The innovation of ISFETs within the domain of solid-state electrochemical sensors is significant due to their minute dimensions, the capacity for instantaneous detection, and the capacity to function in conjunction with established CMOS methodologies. In terms of structural elements, ISFETs substitute a reference electrode for the metal gate of a traditional MOSFET and expose the gate dielectric to the electrolyte solution. A sensitive membrane, such as silicon dioxide (SiO_2), tantalum pentoxide (Ta_2O_5), aluminum oxide (Al_2O_3), or silicon nitride (Si_3N_4), is placed over the gate dielectric. The process of ion exchange occurs at the interface when an aqueous solution comes into contact with the surface, thereby altering the surface potential and, consequently, the threshold voltage (V_{th}) of the transistor [24].

The ISFET function is predicated on surface potential modulation at the electrolyte-sensing membrane interface. It has been demonstrated that the presence of an aqueous environment can induce the formation or dissociation of surface hydroxyl groups. The phenomenon under investigation is attributed to chemical interactions occurring at the dielectric surface. The focal point of this study is the dielectric surfaces of SiO_2 , Si_3N_4 , Al_2O_3 , and Ta_2O_5 . The phenomenon can be better explained by the site-binding model, which is a technique used to explain surface reactions of this kind [25]:



These equilibria produce a net surface charge that alters the electrostatic potential at the gate interface. This shift changes the transistor's threshold voltage (V_{th}). Because of this shift, ionic concentrations can be directly sensed and converted into a quantifiable change in the drain-source current (I_{DS}). According to the Gouy-Chapman and Helmholtz models, the formation of an electrical double layer at the membrane/electrolyte interface impacts the electrical behavior of the ISFET. This interfacial structure consists of two layers: a diffuse Gouy-Chapman layer of counterions and a compact Helmholtz layer of adsorbed ions. Both layers affect the system's total capacitance. Consequently, the effective gate voltage (V_G') of the transistor channel is expressed as follows [26]:

$$V_G' = V_G - V_{Chemical} = V_G - (\gamma + \alpha S_N pH) \quad (2)$$

where, V_G is the applied gate voltage, S_N is the ideal Nernstian sensitivity (59.2 mV/pH at 25 °C), γ is an offset constant, and α accounts for deviations from ideal behavior.

The resulting drain-source current in the saturation regime is governed by:

$$I_{DS} = \mu C_{ox} \frac{W}{L} [(V_{GS} - V_{th})V_{DS} - \frac{1}{2}V_{DS}^2] \quad (3)$$

where, μ is the carrier mobility, C_{ox} is the gate oxide capacitance, and W/L denotes the channel width-to-length ratio. Variations in local ion concentrations modify the interfacial potential, thereby inducing shifts in V_{th} and subsequently in I_{DS} , which can be accurately quantified [26].

It is important to know the two ways that ISFET sensitivity can go above the Nernstian limit (59.2 mV/pH). Material/interface-driven enhancement includes things like defect-mediated adsorption, quantum capacitance, and multi-

site proton exchange. Two examples are nanocrystalline graphene (140 mV/pH) and MoS₂. The way devices are made to work is what architecture and capacitive gain effects are used for. For example, capacitive coupling in dual-gate setups can raise the chemical input to 720.7 mV/pH. On the other hand, floating-gate structures make the device more sensitive by adding charge. This difference is very important: Architecture-driven amplification depends on the electrical setup, while material-driven enhancement depends on the chemistry at the interface. There are rules for each of these about what materials can be used, how hard the process of making them can be, and how well the application fits [26].

Additional capacitive components must be considered when a passivation layer is placed above the gate dielectric in CMOS-compatible ISFET architectures. The diffuse layer (C_{Gouy}), Helmholtz layer (C_{Helm}), and passivation layer (C_{Pass}) contribute to total interfacial capacitance. These components determine the device's sensitivity and temporal response [27]. In contrast to conventional MOSFETs, Figure 1 illustrates the fundamental schematics and operational principles of ISFETs. The ISFET replaces the metal gate of a MOSFET with a reference electrode and an ion-sensitive membrane submerged in the target solution, as illustrated in Figures 1(a) and 1(b). In this configuration, the device utilizes fluctuations in the source-drain current to discern variations in ion concentrations, such as pH. The Gouy-Chapman theory and the site-binding model elucidate the processes by which the electric double layer and ion pairs are formed at the oxide-electrolyte interface, thereby modulating the ISFET's

threshold voltage (V_{th}) and surface potential. Figure 1(c) presents a simplified circuit diagram of an ISFET sensing system, emphasizing the linear relationship between the gate-source voltage (V_{GS}) and the drain-source current (I_{DS}) in the saturation region. Furthermore, Figure 1(d) illustrates the capacitance model of an unaltered CMOS-processed ISFET, emphasizing the roles of the passivation, Gouy-Chapman, and Helmholtz layers in pH sensing. The integration of these diagrams enables a comprehensive evaluation of the structural composition and operational mechanism of the ISFETs. This overview provides a foundation for understanding its applications in biosensing [27].

A unified comparison framework was provided to facilitate a systematic and coherent evaluation of the various ISFET technologies examined in this review. In the next sections, we will use a standard set of performance metrics to rate each gate material, nanostructure, and device architecture. These important parameters are: (i) pH sensitivity (mV/pH), which should be compared to the Nernstian limit (59.2 mV/pH at 25 °C); (ii) long-term stability and signal drift; (iii) response time; (iv) selectivity toward target ions or biomolecules; (v) fabrication complexity and compatibility with standard CMOS processes; (vi) limit of detection (LOD) for biosensing applications; and (vii) hysteresis and temperature dependence. This framework is designed to facilitate the comparison of various material systems and structural configurations for readers. This will help you think critically about the good and bad points of these biosensing applications.

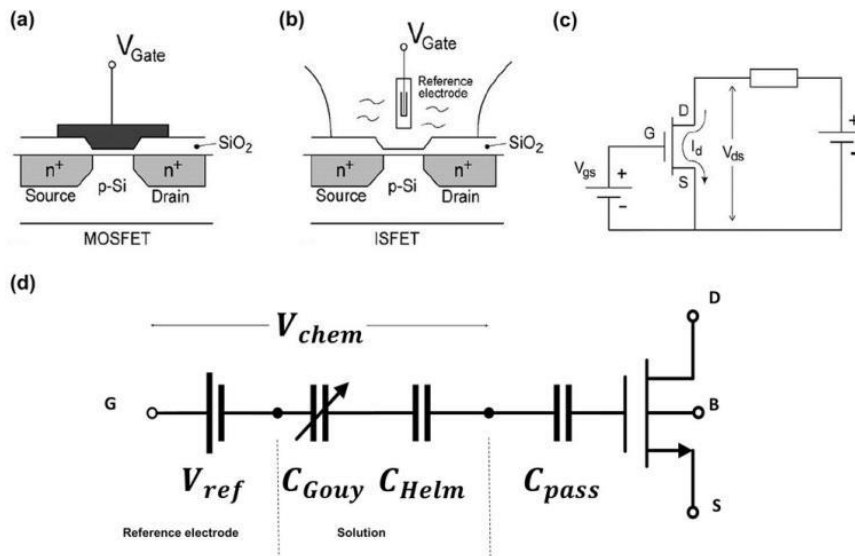


Figure 1. Comparative architectures and models of MOSFET and ISFET devices for pH sensing [27] (a) MOSFET architecture; (b) ISFET architecture; (c) circuit implementation; (d) CMOS-compatible capacitance model

Note: Metal-oxide-semiconductor field-effect transistor (MOSFET), ion-sensitive field-effect transistors (ISFETs), complementary metal-oxide-semiconductor (CMOS)

3. GATE MATERIALS OF ISFETS

The performance of an ISFET is predominantly influenced by the material composition of the gate dielectric/insulator, which functions as the sensitive layer that comes into direct contact with the analyte solution. The capacity of these materials to modulate the gate potential through surface charge interactions facilitates the conversion of chemical signals into quantifiable electrical outputs. Following the advent of Bergveld's inaugural SiO₂-based ISFET, significant progress

has been made in the domain of gate material selection and enhancement. The present research is focused on three primary domains: 2D materials, nanostructured functionalized materials, and thin-film sensitive layers [28].

The material of the gate in ISFETs plays a pivotal role as the critical interface between the semiconductor device and the analyte solution. This interface exerts a direct influence on the device's overall performance, sensitivity, and selectivity. The molecules comprising the ion-sensitive membrane act as transducers, thereby transforming biological changes,

primarily in ion concentrations, into observable electrical impulses. The material composition of the gate exerts a substantial influence on several critical parameters, including responsiveness time, biocompatibility, signal stability, pH responsiveness, and susceptibility to environmental drift.

In general, ISFETs exhibit structural similarity to MOSFETs composed of metal-oxide semiconductors. However, these transistors undergo a modification process that involves the addition of a chemically sensitive membrane, which replaces the traditional metal gate. When immersed in an electrolyte solution and biased across a reference electrode, Ag/AgCl, this membrane modulates the channel current based on changes in surface potential resulting from ionic interactions. As delineated by the Nernst equation, this surface potential is susceptible to ionic activity, thereby establishing a direct pathway for converting the chemical signal into an electrical signal. The evolution of ISFET has encompassed a diverse array of gate materials, transitioning from conventional dielectric oxides to more nanostructured and 2D materials. These materials can be categorized into three primary groups: sensitive thin films, other nanostructured materials, and 2D materials. Each category exhibits distinct advantages in terms of material properties, fabrication compatibility, and applications [29].

3.1 Sensitive thin films

Sensitive thin films are among the most widely used gate materials in ISFETs due to their facile integration into CMOS processes and their reliable electrochemical properties. These materials, which are typically metal oxides or nitrides such as SiO₂, Ta₂O₅, Al₂O₃, and Si₃N₄, act as ion-sensing interfaces that adjust the surface potential in response to changes in ion concentration, particularly protons, in pH sensing. The stability, reproducibility, and tunable sensitivity of these sensors render them optimal for a broad spectrum of biosensing applications [30].

3.1.1 Silicon dioxide (SiO₂)

The employment of silicon dioxide (SiO₂) as a prevalent gate dielectric in ISFETs has emerged as a noteworthy development. This development can be attributed to the material's compatibility with CMOS processes. However, its moderate pH sensitivity (30–40 mV/pH) and surface instability upon prolonged exposure to ionic solutions have motivated the development of stacks containing high-k dielectrics, such as HfO₂ and Al₂O₃, to improve performance [31].

3.1.2 Tantalum pentoxide (Ta₂O₅)

Ta₂O₅ demonstrates low hysteresis, adequate chemical stability, and pH sensitivity that approximates Nernstian behavior (58 mV/pH). Since its initial implementation in the early 1980s as an ISFET gate dielectric, it has been recognized as one of the most reliable materials for pH sensing in environmental and clinical settings [32].

3.1.3 Aluminum oxide (Al₂O₃)

Al₂O₃ exhibits elevated chemical robustness, as demonstrated by its notable resistance to ionic diffusion and wetting. It is noteworthy that this material demonstrates high pH sensitivity and stability, even for small-area sensors, rendering it suitable for highly integrated sensor arrays. The pH sensitivity of an extended-gate ISFET (EG-ISFET) with an

Al₂O₃ sensing layer is approximately 51.2 mV/pH, as demonstrated in Figure 2(a). This sensitivity demonstrates stability even in the context of miniaturized sensing areas. The design's reliability and scalability are ensured by its adequate linearity and chemical stability, rendering it suitable for integrated biosensing applications [33].

3.1.4 Silicon nitride (Si₃N₄)

Research has demonstrated that SiN₄ exhibits superior chemical resistance, water impermeability, and mechanical robustness. Its application has been extensively utilized in the domains of pH measurement and real-time DNA sensing systems. GaN and InN represent two additional nitrides that have demonstrated considerable potential. The development of a CMOS-compatible ISFET integrated with a Si₃N₄ gate for real-time DNA detection is depicted in Figure 2(b). The device under consideration utilizes pH sensitivity during the incorporation of nucleotides, thereby facilitating label-free detection of DNA amplification. The platform's integration with on-chip signal amplification circuitry renders it particularly well-suited for point-of-care genetic testing and lab-on-chip diagnostics. This integration is pivotal in ensuring the system's resilience and adaptability for biomedical analysis by facilitating scalable sensor arrays and high-resolution measurements [34]. The accumulation of electrons on the surfaces of InN-based ISFETs has been shown to result in a significant degree of pH sensitivity and rapid response times, as shown in Figure 2(c) [35].

In the context of ISFET applications, alternative oxide materials such as ZnO, HfO₂, and IGZO have garnered increased attention in recent years. The underlying factors contributing to this heightened level of interest are their exceptional mechanical and electrochemical properties. Although HfO₂ has been demonstrated to effectively reduce oxygen vacancies, thereby enhancing surface stability, ZnO exhibits a wide pH sensing range with high linearity. Amorphous oxide semiconductors, including IGZO and IZO, possess a high degree of mechanical flexibility, rendering them particularly well-suited for integration into flexible and portable biosensor platforms [36]. In addition, due to their chemical tunability and biocompatibility, polymers and organic materials, including polyaniline (PANI), polyethyleneimine (PEI), and polyvinyl chloride (PVC), are utilized as functional gate layers [37]. The processes of multi-ion detection and enzyme immobilization are facilitated by these substances. Structures such as PANI/DNNSA have demonstrated reliability in operation under high humidity conditions and facilitate sensitive detection of analytes such as hydrogen peroxide via enzymatic redox reactions, as shown in Figure 2(d) [38].

3.2 Two-dimensional materials

2D materials have emerged as promising gate materials for ISFETs, owing to their atomically thin structure, high surface-to-volume ratio, and exceptional electrical properties. These characteristics enable heightened sensitivity to surface charge fluctuations, rendering them optimal for the detection of low ion and biomolecule concentrations. Materials such as graphene, black phosphorus (BP), molybdenum disulfide (MoS₂), and MXenes have demonstrated considerable potential in enhancing the performance of ISFETs in biosensing applications [39].

The integration of 2D materials has been demonstrated to

enhance the performance of ISFETs. This enhancement is predominantly attributed to the inherent properties of 2D materials, which encompass their substantial surface areas, ultrathin structures, and adaptable electronic characteristics. These characteristics facilitate enhanced charge interaction at the electrolyte interface, thereby augmenting ISFET performance. ISFETs for selective ion detection have extensively explored graphene due to its remarkable carrier

mobility and surface sensitivity. Sensitivities greater than 60 mV/decade have facilitated the detection of ions, including K^+ , Na^+ , and Co^{2+} . This advancement has been made possible by the functionalization of molecules such as L-phenylalanine or ion-selective membranes. It has been demonstrated that, due to its engineered properties, nanocrystalline graphene has exhibited noteworthy super-Nernstian pH sensitivity, reaching a maximum of 140 mV/pH as shown in Figure 3(a) [40].

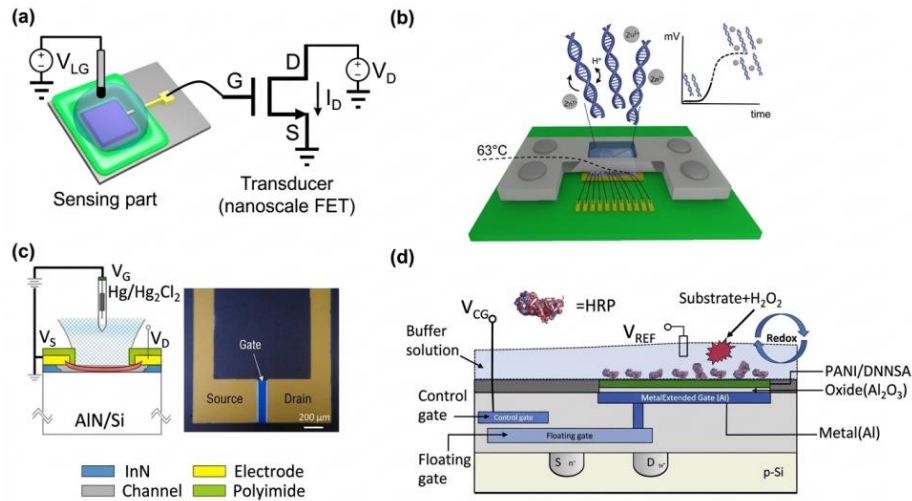


Figure 2. Different sensitive thin-film gate materials of ion-sensitive field-effect transistors (ISFETs) design (a) The nanoscale FET-based extended-gate biosensor with an Al_2O_3 layer [33], (b) a CMOS-integrated Si_3N_4 ISFET for real-time DNA sensing [34], (c) Schematic of a 10-nm-thick InN ISFET [35], and (d) Cross-sectional view of an ISFET modified with PANI/DNNSA layer for H_2O_2 sensing [38]

BP, a promising 2D semiconductor, exhibits both strong surface reactivity and a tunable bandgap. In the domain of biosensing, BP-Au nanoparticle hybrids have demonstrated remarkable sensitivity in the detection of immunoglobulin G (IgG) and arsenic (As^{3+}), along with a rapid response time and a straightforward fabrication process [41]. MoS_2 has been utilized in multilayer gate stacks due to its semiconducting properties and environmental stability. These qualities enable its application in sensitive, drift-free, and current-responsive detection of pH, glucose, and mercury ion (Hg^{2+}) [42]. $Ti_3C_2T_x$ [43] and other MXenes [44] represent a novel class of 2D materials that possess hydrophilic surfaces and high electrical conductivity, thereby facilitating the attachment of biomolecules. Hybrid MXene-graphene ISFETs have been demonstrated to exhibit a femtogram-level detection limit and a 50-millisecond response time, thus enabling their effective utilization for ultra-sensitive biosensing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike proteins.

A summary of typical ISFET configurations using 2D materials is shown in Figure 3. For Co^{2+} detection, the first example is a graphene ISFET functionalized with L-phenylalanine. The second illustration is a hybrid ISFET made of BP and Au specifically for IgG detection. A hybrid dielectric gate based on MoS_2 for high-resolution pH sensing is the third example [45]. The fourth illustration is a $Ti_3C_2T_x$ MXene-graphene ISFET that exhibits high-speed, label-free operation for the detection of the SARS-CoV-2 spike protein. These arrangements highlight the adaptability and enhanced sensing power of 2D material-based ISFETs in biomedical applications.

3.3 Nanostructured gate materials

SiNWs demonstrate superior surface-to-volume ratios, thereby enhancing analyte interaction and increasing sensitivity. The SiNW-based ISFETs have demonstrated excellent signal-to-noise ratios and pH resolutions as low as 0.016 pH. In addition, it has been demonstrated that functionalized SiNWs can be utilized for the detection of multiple ions [46]. CNT-based ISFETs demonstrate high transconductance, attributable to their conduction characteristics that are analogous to those of electronic connections in high-speed communication networks. Aligned CNT arrays have demonstrated effective detection of K^+ and glucose, as well as super-Nernstian responses (943 mV/pH). In order to enhance signal readout, CNTs have also been utilized as hybrid components or ion-selective transducers [47]. In order to enhance ion interaction sites, researchers have employed the utilization of ZnO nanorods, V_2O_5 nanoribbons, and analogous 1D structures.

The gate's material has a big effect on the trade-offs in ISFET performance. CMOS works well with standard thin films like Ta_2O_5 and Al_2O_3 . They have stable near-Nernstian sensitivity, but they can only handle 59 mV/pH and can drift. Graphene and MoS_2 are 2D materials that are very sensitive and respond super-Nernstianly, but they are hard to make in a way that is always the same. Nanostructured materials like SiNWs and CNTs have high surface-to-volume ratios that make it easier to find things, but they also make things more complicated. You can choose the best material for your needs by looking at the trade-offs between sensitivity, stability, and manufacturability in Table 1. The analysis reveals clear trade-offs across gate material categories. Conventional thin films

offer stable near-Nernstian sensitivity and CMOS compatibility but suffer from long-term drift. 2D materials enable super-Nernstian sensitivity at the cost of fabrication variability and scalability challenges. Nanostructured

materials achieve ultra-low detection limits but face integration difficulties. Critically, no single material satisfies all application requirements; selection depends on the specific balance of sensitivity, stability, and manufacturability required.

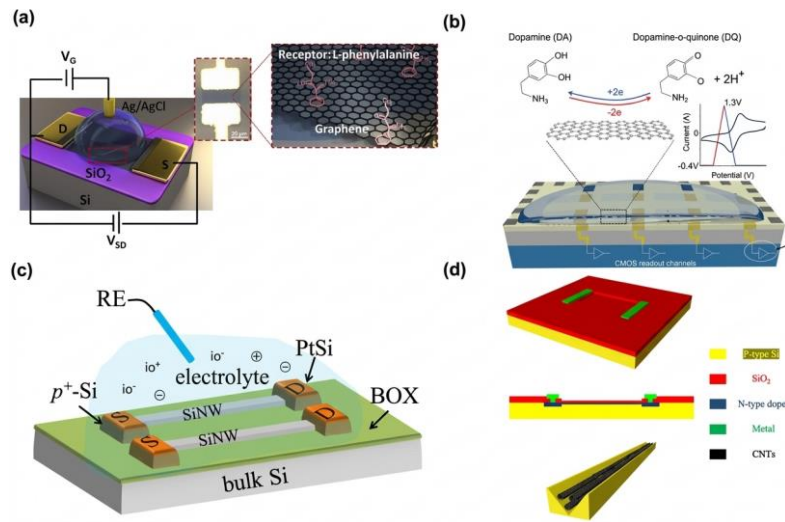


Figure 3. Different nanostructured with 2D gate materials of ISFETs transistors (a) ISFETs based on graphene and the L-phenylalanine receptor [40], (b) CMOS graphene sensor arrays for dopamine molecules sensing [44], (c) 3D of silicon nanowire (SiNW) based ISFETs [46], and (d) CNT-based ISFETs for pH sensing devices [47]

Note: Ion-sensitive field-effect transistors (ISFETs), complementary metal-oxide-semiconductor (CMOS), carbon nanotube (CNT)

Table 1. Performance comparison of ISFET devices based on different sensitive layers and gate materials

| Ref. | ISFETs Types | Gate Materials | Sensitivity | Stability/Drift | Response Time | CMOS Compatible | Fabrication Complexity | Application (Target) |
|------|---|--|------------------|-----------------|------------------|-----------------|------------------------|-------------------------------|
| [6] | Nanoporous-layer ISFET / EGFET | SiO ₂ , Si ₃ N ₄ , Al ₂ O ₃ , | 19–58 mV/pH | High | Moderate–Fast | Yes | Moderate–High | Biosensing (proteins) |
| [48] | Graphene-based ISFET (G-ISFET) | Graphene | 152.4 mV/dec | High | Fast (real-time) | Yes | Moderate | Sodium sensing |
| [49] | Dual-gate ISFET (In ₂ O ₃ nano-channel) | In ₂ O ₃ + Ta ₂ O ₅ / Si ₃ N | 321.5 mV/pH | Low | Fast | Potential | Moderate | pH sensing |
| [50] | Graphene-based ISFET array | Graphene | 52–55 mV/pH | High | Fast | Potential | Moderate | Chemical sensing, food safety |
| [51] | Conventional ISFET | Al ₂ O ₃ , Si ₃ N ₄ | 54.6–59.17 mV/pH | High | Fast | Yes | Moderate | pH sensing |
| [52] | Gold-coated SiNW ISFET | Au / Si Nanowire | 44 mV/decade | Moderate | < 20 s | Yes | High | Na ⁺ |

Note: Ion-sensitive field-effect transistors (ISFETs), complementary metal-oxide-semiconductor (CMOS)

4. GATE STRUCTURE OF ISFETs

The gate structure of ISFETs exerts a substantial influence on their functionality, performance, and integration potential. A wide array of gate designs exists. The objective of these designs is to enhance sensitivity, stability, reusability, and compatibility with CMOS, in addition to other characteristics. A comprehensive review of the extant literature has yielded four primary categories of gate structures: floating-gate ISFETs (FG-ISFETs) [53], extended-gate ISFETs (EG-ISFETs), dual-gate configurations, and unmodified CMOS gates. With regards to signal amplification, fabrication complexity, and miniaturization, each architecture presents a distinct set of benefits and trade-offs.

4.1 Unmodified CMOS gate ISFET structures

Integrated circuits with a semiconductor-metal-semiconductor (S-M-S) ISFET fabricated through unmodified CMOS processes permit large-scale integration and cost-effective manufacturing, thereby eliminating the necessity for post-CMOS modifications. In these devices, the gate metal is removed and replaced by a passivation layer (Si₃N₄ or SiO₂), which interfaces directly with the electrolyte. The ion-sensitive gate potential is capacitively coupled through this layer to the underlying MOSFET channel. In addition to facilitating pH sensing, this structural element has been incorporated into platforms for DNA detection and microbial analysis. However, concerns regarding threshold voltage drift, attributable to trapped charges, and signal attenuation resulting

from thick passivation layers persist. Thermal annealing or UV treatment has been demonstrated to alleviate these problems to a certain extent. Figure 4(a) illustrates an ISFET structure derived from an unmodified CMOS process, wherein the metal gate is substituted by a passivation layer (Si_3N_4) that interfaces with the analyte solution. The application of gate bias by a reference electrode is followed by alterations to the threshold voltage due to ion interactions at the surface, enabling sensing [54].

4.2 Dual-gate ISFET structures

Dual-gate ISFETs are composed of two gates: a top sensing gate and a bottom control gate. It is noteworthy that these gates are frequently separated by an insulating layer. The capacitive coupling between the gates has been demonstrated to enhance the control of the channel potential. This enhancement in sensitivity exceeds that of single-gate designs. In a recent presentation, Zhou and his team unveiled a novel electronic sensor, which they have designated as an ISFET. The sensor in question features a dual-gate silicon nanowire (SiNWs). This sensor possesses the capacity to discern minute variations in pH. The device demonstrates a high degree of sensitivity, with a measuring range of 720.7 mV/pH. This outcome exceeds the Nernstian limit, which is defined as the upper threshold of quantifiable phenomena. This objective was accomplished by means of a capacitive amplification mechanism. Furthermore, Yen and his team discovered that the sensitivity of the oxide to thickness is contingent upon the precision of the dielectric engineering. This configuration has

proven particularly effective in the detection of low-level substances within the body, such as prostate-specific antigen (PSA). A dual-gate ISFET, as illustrated in Figure 4(b), employs a bottom control gate situated beneath the channel and a top sensing gate exposed to the analyte to enhance electrostatic control and sensing performance. The capacitive coupling of these gates, in conjunction with the separation of the gates by dielectric layers, facilitates the modulation of the channel potential by the top gate with enhanced efficacy [55].

4.3 Extended-gate and floating-gate ISFET structures

The enhancement of modularity, sensitivity, and integration capabilities of ISFET-based biosensors can be achieved through the implementation of two methodologies: EG-ISFETs and FG-ISFETs. In EG-ISFETs, the chemically sensitive membrane is separated from the MOSFET channel. The substance is then applied to a distinct electrode. The electrode is electrically connected to the gate pad of a standard MOSFET. This design facilitates the replacement and reuse of the sensing layer while protecting the electronics from chemical exposure. Electrochemical impedance spectroscopy (EIS) has a variety of applications, including pH sensing and ion detection. A substantial body of research has demonstrated that materials such as Al_2O_3 , ZnO, and Ta-doped ZnO exhibit consistent and predictable responses. The efficacy of these sensors when used with commercial CMOS has been demonstrated, and they are straightforward to manufacture, rendering them well-suited for incorporation into low-cost biosensor designs [56].

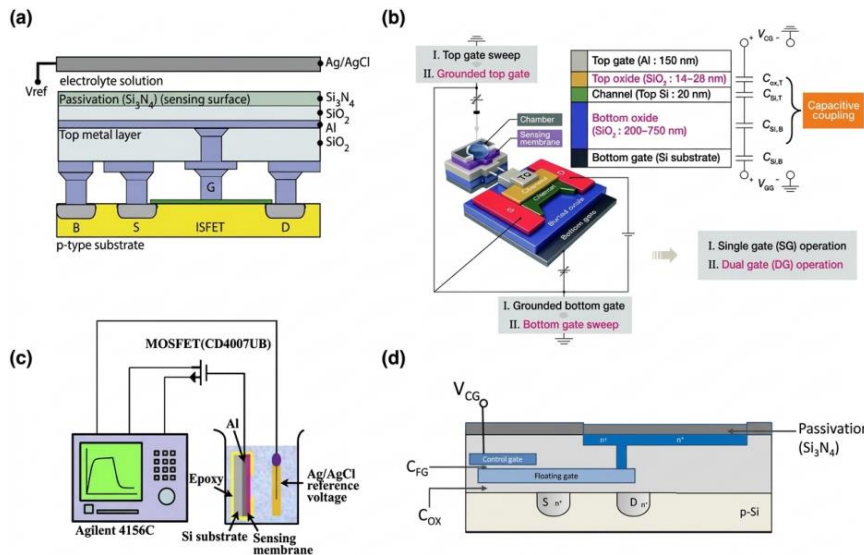


Figure 4. Gate structures of ISFETs devices for bio-sensing applications (a) Unmodified CMOS, (b) Dual-Gate, (c) Extended-Gate, and (d) Floating-Gate structures [46]

Note: Ion-sensitive field-effect transistors (ISFETs), complementary metal-oxide-semiconductor (CMOS)

In contrast, FG-ISFETs employ a gate configuration in which the sensing electrode is linked to a floating gate. The floating gate, a critical component of the system, functions by regulating the channel conductance. This configuration enables its operation in the absence of a reference electrode, a feat that can be accomplished through the utilization of conventional CMOS technology. The floating gate facilitates the integration of the charge, thereby enabling the reliable and stable transmission of signals. The employment of specific materials, including polyaniline (PANI) composites, has been demonstrated to enhance the sensor's capacity to detect

particular targets, such as H_2O_2 or enzymatic reactions. The efficacy of FG-ISFETs has been demonstrated in high-density biosensor arrays and ultra-low power applications, particularly in wearable or implantable biomedical systems. As shown in Figure 4(c), the EG-ISFET design uses a sensing electrode that is different from the MOSFET. This design makes it easy to replace the membrane, reduces manufacturing costs, and ensures that it works with CMOS. As shown in Figure 4(d), an FG-ISFET uses capacitive coupling to an isolated gate. This makes stable, reference-free operation possible. This setup is especially good for low-power biosensing applications [57].

The ISFET gate architecture has a direct impact on the balance between how well it works and how hard it is to put together. Unmodified CMOS lets you make more of something, but it has problems with drift and signal loss. In dual-gate setups, capacitive amplification is used to get sensitivity that goes beyond the Nernst limit. This makes them great for very sensitive detection, even though they are harder to use. With extended-gate designs, you can use electronics that can be reused and modular for sensors that you throw away. You don't need reference electrodes for low-power, high-density arrays when you use floating-gate architectures. Table 2 shows how these trade-offs work together to show that the best architecture depends on what the application needs. New hybrid methods are putting together more and more structures in next-generation biosensing platforms to get

around the limits of each one. Each type of gate architecture has its pros and cons. CMOS gates that haven't been changed are cheap and easy to scale, but they have problems with signal loss and drift. Because of capacitive amplification, dual-gate configurations are the most sensitive. However, they are hard to design and not good for arrays with low power or high density. Extended-gate structures are modular and protect electronics, but parasitic capacitance can make signals less reliable. Floating-gate architectures can work without a reference electrode and with low-power arrays, but they have trouble holding charges. Ultimately, the architecture selection must align with the application's requirements, which may include sensitivity, stability, modularity, or power consumption [58].

Table 2. Overview of ISFET devices with different gate structures and their bio-sensing applications

| Ref. | Gate Structures | Gate Materials | Sensitivity Enhancement | Key Features | Pixel Array | Applications |
|------|--------------------------------------|--|--|---|----------------------|---|
| [5] | Single gate ISFETs | Si ₃ N ₄ , Ta ₂ O ₅ , Al ₂ O ₃ | Baseline (40-58 mV/pH) | Simple structure, CMOS compatible, moderate sensitivity | Single 16 × 16 | Sweat pH monitoring and Ion detection |
| [8] | Extended-gate ISFET | HfO ₂ -coated Al | 55 mV/pH | CMOS-compatible, low drift | --- | Phenol detection, chemical sensing |
| [59] | Extended gate ISFETs | ZnO: Ta, TiO ₂ , MoS ₂ / Al ₂ O ₃ | Super-Nernstian (up to 720 mV/pH via capacitive amplification) | Replace gate, Isolated electronics, and reusable FET sections | 4 × 4 to 32 × 32 | Glucose and ethanol sensing |
| [60] | Floating gate ISFETs | SiO ₂ , PANI, HfO ₂ | Moderate to high (44-58 mV/pH) | No reference electrode needed, and good free detections | 78 × 56 to 512 × 576 | DNA/protein detection, and pH sensing |
| [61] | Negative-capacitance dual-gate ISFET | SiO ₂ , HfO ₂ | 654 mV/pH) | Super-Nernstian response, reduced drift and hysteresis | --- | Highly sensitive pH detection and enzyme activity |

Note: Ion-sensitive field-effect transistors (ISFETs), complementary metal-oxide-semiconductor (CMOS)

5. INSTRUMENTATION AND READOUT CIRCUITS

Modern ISFET-based systems need advanced instrumentation methods to meet system-level needs. To reduce common-mode noise, drift, and temperature changes, differential measurement methods often compare the sensing ISFET. Also, pH-to-time conversion methods change chemical signals into time or frequency domains, which are less likely to be affected by noise and changes in the process. So, they use less energy than normal voltage-domain reading. Adding on-chip analog-to-digital converters (ADCs), especially sigma-delta and successive approximation registers (SAR) architectures, allows for smaller system-on-chip implementations that further improve signal resolution. Digital correction, periodic reference, and offset cancellation are also important auto-calibration methods that help keep devices from drifting and mismatching over time. These methods improve accuracy, stability, and scalability, but they also add design overhead, use more power, and make circuits harder to understand [62].

The architecture of the ADC you choose has a big effect on how well the whole system works. ADCs that use sigma-delta ($\Sigma\Delta$) have a high resolution (usually 16–24 bits) and built-in noise shaping. This makes them great for sensing tasks that don't need a lot of bandwidth but do need a lot of accuracy. But they need oversampling and complicated digital filtering, which uses more space and power. ADCs with SAR are a good choice because they have a lot of useful features. They have a

medium resolution (8–16 bits), don't use much power, and don't take up much space. This is why they work well for ISFET arrays with a lot of channels and a lot of density. The resolution tells you how small a pH change you can find. With 12-bit resolution, you can see a change of about 0.01 pH, but only in the best conditions [63].

Integration creates more problems at the system level that need to be dealt with correctly. An ADC on a chip lowers noise sensitivity and makes it possible to make smaller system-on-a-chip (SoC) designs by lowering parasitic capacitance and the length of signal routes. But it makes the chip bigger and harder to build. Off-chip readout gives you more options and makes prototyping easier, but it also adds parasitic and noise sources to the interconnects that can make signals less clear, especially in high-density arrays where routing congestion is bad. Digital switching noise is a constant problem for fragile analog front-ends. Separating, protecting, and timing the two signals carefully can fix the problem. To make up for differences in devices, changes in temperature, and aging over time, you need to use methods like offset cancellation, frequent reference sampling, and digital correction. These calibration methods make things more accurate, stable, and scalable, but they also make design and power costs go up, which means that each application needs to be adjusted for. These factors related to instrumentation show that the design of the readout circuit is very important for the performance of the whole system. It has a direct effect on power use, scalability, sensitivity, and resolution [64].

6. ISFETS FOR BIOSENSING APPLICATIONS

ISFETs are experiencing a surge in popularity in sophisticated biosensing applications, including drug development, environmental monitoring, clinical diagnostics, and wearable medical technology. The conversion of biochemical interactions into electrical signals is enabled by ISFETs. These devices are distinguished by their rapid response time, small size, and compatibility with CMOS fabrication processes. These properties render ISFETs promising candidates for utilization in bioelectronic interfaces of the future [65]. There are four primary categories of ISFET-based biosensing applications: inorganic ion detection, nucleic acid sensing (DNA/RNA), protein detection, and microbe monitoring. Each category utilizes the advantages inherent to ISFETs, including high sensitivity, label-free detection, and the capacity for seamless integration with microfluidics and readout electronics. This integration facilitates real-time, low-power, high-throughput analysis [66].

Despite the demonstrated performance of ISFET-based systems across various applications, several system-level bottlenecks remain. These include signal drift and hysteresis affecting long-term stability, limited selectivity without functionalization layers, susceptibility to environmental noise and temperature variations, and challenges in large-scale integration and calibration. Additionally, trade-offs between sensitivity, response time, and fabrication complexity constrain practical deployment. Addressing these bottlenecks requires coordinated optimization of device architecture, material selection, and signal conditioning circuits [67].

ISFET-based systems have come a long way, but there are still problems with them in every area where they are used. Some of these problems are signal drift and hysteresis, limited selectivity in complex biological matrices, sensitivity to changes in temperature and environmental noise, surface damage from biofouling, and problems with large-scale integration and calibration. These limits are not universal; instead, they represent interdependent trade-offs that vary with the materials and designs employed. The following sections will discuss specific biosensing applications in greater detail, highlighting recent advances as well as the challenges that must still be addressed before practical implementation can be realized.

6.1 Inorganic ion sensing

ISFETs are very good at detecting inorganic ions such as (K^+ , Na^+ , Ca^{2+} , Cu^{2+} , and Cl^-). These are important for our bodies and the environment. These ions are very important for electrolyte balance, neurological function, and cardiovascular health. For example, a special kind of sensor called an ISFET that uses graphene and is modified with potassium ionophores can detect very small amounts of potassium, as low as 10 nanomoles (about 40 millionths of a liter). This makes it useful for medical testing because it allows the sensor to monitor things as they happen. In a similar way, a Si-nanoribbon ISFET with a glycine, glycine, histidine peptide layer allowed for the selective detection of Cu^{2+} through changes in surface charge interactions [68]. The materials used in the gate, like Al_2O_3 or HfO_2 , and the membranes are very important in determining how well the ISFETs can separate ions and how sensitive they are.

6.2 Nucleic acid sensing (DNA/RNA)

ISFETs are particularly good at monitoring the process of DNA and RNA combining and multiplying. This process involves the release of protons when nucleotides are added, which changes the local pH level. Moser and his team created a platform that can detect DNA amplification in real time. This platform uses CMOS technology and an ISFET array. Lab-on-chip systems that use ISFET technology have been used to detect mutations associated with breast cancer and microRNA (miRNA) biomarkers, such as Let-7b, with a detection limit as low as 1 nmol [69]. These advances show that ISFETs are good for molecular diagnostics, especially in portable or low-resource settings.

6.3 Protein detection

The detection of proteins using ISFETs generally necessitates the functionalization of the sensing surface with antibodies or receptors, thereby facilitating real-time monitoring without the requirement of labeling. PSA in human plasma can be detected using a nanoribbon-based ISFET with a wide dynamic range (10 pM–1 μ M) [70]. The process of protein binding has been demonstrated to induce alterations in the surface charge, thereby impacting the flow of electrical current. This sensitivity facilitates the diagnosis of early-stage cancer and inflammatory diseases.

6.4 Microbial monitoring

Furthermore, ISFETs have been utilized for the monitoring of microbial activity, encompassing bacteria, fungi, and viruses. Forouhi and Ghafar-Zadeh [71] developed a 65-nm CMOS ISFET platform, thereby making a significant contribution to the field of nanotechnology. This platform is capable of measuring the pH level. The device is capable of converting the pH level into a quantitative measurement. The reading is indicative of the quantity of *E. coli* in a liquid medium containing living organisms. The testing was conducted on a range of 14 to 140 colony-forming units (CFU) per milliliter (mL) of *E. coli*. This approach facilitated the discernment of the distinguishing characteristics of the bacteria present within the samples collected. The detection of metabolic byproducts, such as H^+ ions, which are produced by microbial respiration, is facilitated by ISFETs. This approach ensures a reliable measurement of microbial growth, despite its indirect nature. In addition, ISFET-based systems have been employed for the detection of *Salmonella typhimurium* and the Influenza A virus through the use of immobilized recognition elements. These offer expeditious, label-free alternatives that are analogous to conventional PCR techniques.

As demonstrated in Figure 5, ISFETs demonstrate a high degree of versatility and sensitivity in a variety of biosensing applications. As demonstrated in Figure 5(a), the graphene-based ISFET is engineered to selectively detect potassium ions (K^+). In this configuration, a K^+ ionophore membrane interfaces with the graphene channel. This configuration facilitates real-time monitoring of ion concentration through charge transfer modulation, thereby achieving a detection limit as low as 10 nM. This outcome underscores the paramount importance of high sensitivity and selectivity in the context of electrolyte monitoring in medical diagnostics. As demonstrated in Figure 5(b), a sensing platform for nucleic

acids has been developed, employing an ISFET. In this platform, DNA amplification releases hydrogen ions (H^+), which induce local pH changes. An FG-ISFET is capable of detecting these alterations.

This platform enables the label-free, real-time detection of breast cancer-associated mutations with enhanced signal resolution. As illustrated in Figure 5(c), a nanoribbon ISFET has been developed for the detection of PSA in human plasma in real time. The antibody-functionalized gate selectively binds to PSA, altering the surface potential and modulating the device current. This property facilitates detection within the picomolar to micromolar range, even under conditions of high ionic strength. As illustrated in Figure 5(d), a cancer cell monitoring system based on ISFETs has been developed. This system is capable of detecting pH changes induced by

metabolism at the cell/gate interface. The gate has undergone modification through the adsorption of protein layers, which function as ionic insulators. This facilitates the detection of cellular activity and environmental pH shifts in situ [72].

A comprehensive evaluation of the most recent ISFET-based biosensing applications is provided in Table 3. These applications possess a high degree of sensitivity, enabling the detection of minute quantities of substances. Furthermore, these sensors possess the capacity to detect ions, biomolecules, microbes, and cells. The functionality of these sensors can be attributed to the utilization of disparate materials and designs. These characteristics render them highly versatile, making them suitable for a range of applications, including settings such as clinics, environmental studies, and point-of-care testing.

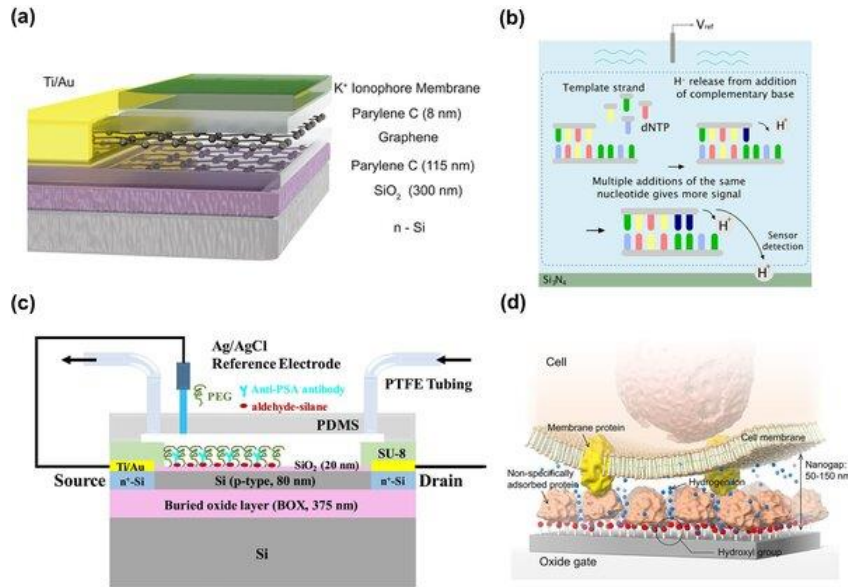


Figure 5. Bio-sensing applications of ISFETs devices [46]: (a) Graphene-based ISFET for selective and real-time detection of K^+ ions, (b) DNA sensing using ISFETs to monitor proton release, (c) Nanoribbon ISFET enabling label-free, real-time detection of PSA, (d) ISFET-based cancer cell sensing through pH variations
 Note: Ion-sensitive field-effect transistors (ISFETs), prostate-specific antigen (PSA)

Table 3. ISFET devices based on biosensing applications with key parameters

| Ref. | Gate Structures | Gate Materials | Sensitivity | Selectivity | LOD | Pixel/Array | Biosensing Applications |
|------|--------------------------|--|-------------------------------|--------------------------|------------------------|------------------|---|
| [73] | ISFET / CMOS integrated) | Si ₃ N ₄ , Al ₂ O ₃ , Ta ₂ O ₅ | High (pH/biomarker dependent) | High (antibody, DNA) | pg/mL – fM range | Arrays | Biomarker detection (cancer) |
| [74] | GFET liquid-gated | Graphene +K ⁺ | 69.8 mV/decade | High (bioreceptors) | fM – aM range | CMOS-compatible | Cancer, neurodegenerative |
| [75] | Nanoribbon FET | Si nanoribbon with Ab | 0.1 μA/log[PSA] | High (antibody-specific) | 10 pM | 1 × 1 | Prostate cancer diagnosis |
| [76] | CMOS ISFETs | Si ₃ N ₄ gate dielectric | Digital pH to time | Species-specific | 14 CFU/mL | 32 × 32 CMOS | Food safety |
| [77] | Ribbon type ISFET | Modified Si | 70 mV/decade | High (with membrane) | 100 nM | Discrete channel | Heavy metal detection in biological systems |
| [78] | Floating gate ISFET | SiO ₂ + PNA probe | 56 mV/pH | High (sequence-specific) | 1 nM | 4 × 4 CMOS | Cancer detections (Breast) |
| [79] | Extended gate ISFET | Al ₂ O ₃ + virus Ab | 50 mV/pH | Species-specific | 10 ⁴ PFU/mL | 2 × 2 array | Viral detection |

Note: Limit of detection (LOD), ion-sensitive field-effect transistors (ISFETs), complementary metal-oxide-semiconductor (CMOS), field-effect transistor (FET)

ISFET biosensors are very flexible and can be used in four main areas: (i) inorganic ion sensing with functionalized graphene can detect nanomolar levels for clinical electrolyte monitoring; (ii) nucleic acid detection with CMOS-integrated

arrays can sequence DNA without labels by releasing protons; (iii) protein detection with nanoribbon ISFETs can detect picomolar levels for early cancer diagnosis; and (iv) microbial monitoring can measure pathogens for food safety and

infectious disease detection.

Table 3 shows three consistent patterns of performance: nanoscale transduction makes things more sensitive, surface functionalization controls selectivity, and CMOS integration makes it possible to detect multiple things at once. These improvements make ISFETs revolutionary tools for point-of-care diagnostics and precision medicine, but only if more progress is made in standardization and long-term reliability.

7. CONCLUSIONS

ISFETs have evolved into one of the most promising platforms for next-generation biosensing technologies. This evolution is driven by their inherent advantages, such as label-free operation, high sensitivity, rapid response time, and compatibility with standard CMOS fabrication. This review offers a thorough examination of recent advancements in the domains of ISFET fabrication, gate material engineering, structural configurations, and application-specific innovations. Significant advancements in gate materials, including high-k dielectrics, 2D nanomaterials such as graphene and MoS₂, and functional coatings such as ionophores and bioreceptors, have led to substantial improvements in the selectivity and sensitivity of ISFET devices. Innovative gate structures, including extended-gate, floating-gate, and dual-gate configurations, have facilitated modularity, reusability, and enhanced electrostatic control. Consequently, these structures have enabled their integration into miniaturized and integrated biosensing systems.

ISFETs are great for clinical, environmental, and wearable diagnostics because they can quickly and accurately find a lot of different biological targets. Biofouling, signal drift, and the fact that things are made differently are just a few of the problems that still make it hard for people to use it often. Different types of architectures deal with drift mechanisms in different ways. Drift mechanisms include things like charge trapping, ion diffusion, and flaws that happen during the process. For instance, unmodified CMOS is unstable but focuses on scalability; extended-gate structures make it more stable; dual-gate structures allow for partial drift compensation; and floating-gate structures make it more sensitive but lower charge retention. These trade-offs show that one design can't improve all three of these things at once. Artificial intelligence-assisted signal processing, flexible substrates, and wireless systems all need to get better in many ways if the future is to move forward. ISFETs will be very important in precision medicine in the future.

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NOMENCLATURE

| | |
|--------------------------------|---|
| Al ₂ O ₃ | Aluminum oxide |
| CMOS | Complementary metal-oxide-semiconductor |
| IDS | Drain-source current |
| ISFETs | Ion-sensitive field-effect transistors |
| L | Channel length |
| SiO ₂ | Silicon dioxide |
| Si ₃ N ₄ | Silicon nitride |
| Ta ₂ O ₅ | Tantalum pentoxide |
| V _{GS} | Gate-source voltage |
| V _{th} | Threshold voltage |

Greek symbols

| | |
|----------|--------------------|
| α | Sensitivity factor |
| γ | Offset constant |
| μ | Carrier mobility |