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Advances in field effect transistor based electronic devices integrated with CMOS technology for biosensing

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A B S T R A C T

This review article embarks on an enlightening journey through the multifaceted realm of electronic devices and their applications in biosensing, emphasizing the role of Field effect transistor (FET) based biosensors and Complementary Metal Oxide Semiconductor (CMOS) processes in biosensing device development. It begins by elucidating the foundational principles of biosensing and underscoring the crucial contribution of transducers, establishing a robust understanding of the field. The article unravels the intricate interplay between electronic biosensors and CMOS processes, offering a concise yet insightful exploration of their operational intricacies, diverse practical applications, and recent advancements. Additionally, it spotlights the pivotal role of FET-based biosensors integrated with CMOS processes in miniaturizing biosensors and thus amplifying their real-world efficacy. Moreover, the role of modern technologies, such as the Internet of Things (IoT), in recent biosensor development has been discussed. By addressing inherent challenges like sensitivity, integration, cost, and accessibility, the article underscores the vital role of biosensing technologies driven by electronic devices in wearable technology development. In addition, integrating these devices to fit with the ongoing trend of VLSI technology faces significant challenges. To overcome this aspect, sensors based on molecularly imprinted polymers (MIPs) can be the best alternative, as they will avoid utilizing bioreceptors, as it simplifies integration by reducing complexity, enhancing stability, and improving compatibility with CMOS processes. Hence, this review's distinct contribution lies in its comprehensive approach, shedding light on how biosensing technologies, underpinned by electronic devices such as FETs and CMOS processes, offer solutions for realizing modern-day devices.

1. Introduction

In the era of electronics and information technology, mankind interacts with a variety of devices daily in the form of smartphones, watches, and healthcare monitoring systems. Among these devices, sensors are one such type, which has upgraded human life through their applications in diverse fields [1]. Sensors, in simple words, are devices that detect changes in source or environment and accordingly, provide usable output in response to the specified quantity. They are frequently categorized based on the input data, applications, and the functioning principle or the type of signal it works on. Based on functioning principles it can be physical sensors, chemical sensors, or biological sensors (Biosensors). A biosensor can be defined as a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles, or whole cells to detect chemical compounds usually by electric al, thermal, or optical signals [2,3]. They are fabricated from three essential components; bioreceptor (recognition element), transducer, and amplifier. The bioreceptor reacts to the specific analyte to provide a biological signal that is essential to any biosensor device. The interaction between the bioreceptor and the analyte result in the process of signal production and this signal can be in the form of light, heat, pH, charge, or mass change [4]. This biological signal is recognized by the transducer, which then converts it into a format that may be used for storage, processing, amplification, and display [1]. Transducers generate either optical or electrical signals through a process of energy conversion called signalization, which is directly linked to the analyte-bioreceptor interaction reaction. Ultimately, the biological signal is amplified and transformed into an electrical format by the amplifier, displaying the information on a microelectronic device [5,6].

Moreover, biosensors exhibit diverse classifications depending on

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bioreceptors, technology, and transducers. In terms of transducers, biosensors can be categorized into electrochemical, optical, electronic, thermal, and acoustic types [4]. Among these, electronic transduction devices play a crucial role in sensing applications owing to their potential for miniaturization, unlike electrochemical, optical, thermal, and acoustic types. Advancements in materials science have facilitated top-down approaches in electronics, allowing for the precise fabrication of nanoscale components essential for miniaturized sensors [7–9]. This miniaturization enables the development of compact and portable sensing devices, revolutionizing fields like healthcare and environmental monitoring. Unlike other transduction techniques, electronic devices offer the versatility to integrate seamlessly into wearable technology, enabling real-time monitoring and improving accessibility to critical information for users [10]. Electronic biosensors employ field-effect transistors (FETs) for their operation. The utilization of FETs offers advantages such as rapid response, integration with Complementary Metal Oxide Semiconductor (CMOS) processes, and implementation of parallel sensing structures, that facilitate the fabrication of ultra-scaled devices [11]. The use of FET-based architectures integrated with CMOS processes allow the incorporation of both digital and analog signal processing, thereby enhancing the sensitivity and performance [12–14]. This integration aligns well with the future of biosensing, capitalizing on the scaling trajectory outlined by Mo ore's law [15] in the VLSI industry. Furthermore, the structural development in FET technology has led to a transition from planar transistors to fin field effect transistors (FinFETs) or gate-all-around FETs (GAAFETs). This transition in recent decades have aided in advancements in CMOS integrated circuits (ICs). Zhang et al. reviewed in detail the recent breakthroughs in transistor design methodologies and structure. Moreover, they have also discussed how the geometrical shrinkage through vertical transistor stacking have taken us beyond Moore's law [16]. These advancements set the stage for intelligent biosensing devices that are seamlessly integrated with Internet of Things (IoT) technology; offering remote excess, data analytics, efficient real-time monitoring, and sustainable practices by optimizing the utilization of resources and waste reduction [7,8]. Biosensors have diverse applications spanning in the field of healthcare, environmental monitoring, and industrial processes, which demonstrates their impact in various sectors, thereby contributing to United Nations Sustainable Development Goals, namely Good Health and Well-being (SDG 3), Clean Water and Sanitation (SDG 6), and Sustainable Cities and Communities (SDG 11) [17–19]. Their significance in the healthcare sector was highlighted in the context of global SARS-CoV-2 pandemic due to label-free and highly sensitive detection potentiality. In this context, Yu et al. presented a comprehensive review on field effect transistor-based biosensor for label free detection of SARS-CoV-2 [20]. Hence, the integration of biosensors with cutting-edge technologies like CMOS and the IoT represents a significant stride toward achieving goals more efficiently and sustainably, aligning with the demands of the current generation. Additionally, to further enhance the stability of the sensing systems without compromising the selectivity, molecularly imprinted polymers (MIPs) can be utilized. MIPs are synthetic receptors which operate by the lock and key mechanism to selectively bind with the targeted molecule with which it is templated during synthesis. MIPs when employed in the sensing system provide specificity and selectivity close to the natural receptors along with enhancing chemical and physical stability. Moreover, MIPs can be successfully used with most type of transduction units including the FETs, in which they are coated on to the gate of the FET. When the potential is applied to the gate, the absorption/desorption through the MIP template affects the net voltage and hence the electrical conduction through the FET [21]. Tsai et al. reported a MIP based ISFET system and used it for the detection of creatinine where MIP was utilized onto the gate electrode [22]. Moreover, these MIP based sensing system exhibits compatibility with CMOS processes, enabling its integration with microelectrode arrays (MEAs) for future applications [23]. Thus, this review article (Fig. 1) aims to describe the FET based device architectures in the form of electronic biosensors utilized in the current years for paving the way forward the next generation of miniaturized wearable biosensors, spanning their applications in interdisciplinary domains. Furthermore, it also highlights how embedding IoT technology with biosensors has shifted the trend toward intelligent biosensing devices along with highlighting the potential of MIPs for fabricating highly selective, stable, and low-cost sensing systems. The current challenges and innovations are also discussed which can drive further application-based innovations in this area. Previous reviews [4,8,12,14,24] have explored in detail about the biosensor technology and their classification, the role of FET-based architectures in specific biological applications or the role of IoT in the area of wearable sensors. However, this review comprehensively examines innovations and challenges, concentrating on electronic transducing systems, and consolidates the fundamental aspects of biosensing systems and prospects under a unified umbrella by exclusively focusing on the electronic device perspective.

2. Biosensors and their classification

Biosensors have advanced significantly in the realm of bio-analysis since Clark and Lyons' [25] demonstration in 1962 of the first biosensor. The introduction of the first commercial biosensor intended to detect glucose in 1975 [26] marked a turning point. The combination of receptors that identify target analytes and transducers, which convert

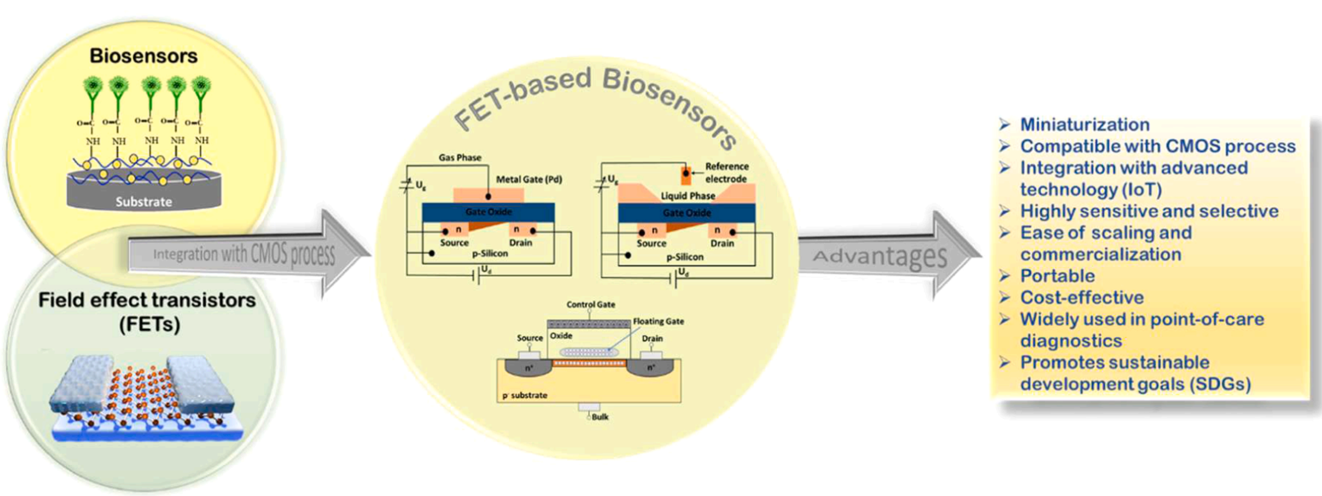

Fig. 1. Overview of this review with advantages of this technology.

this biological interaction into a detectable signal that can be further used, is what defines biosensors [1]. The three primary components of a conventional biosensor are a bioreceptor, a transducer, and an amplifier. Bioreceptors are biological elements that can determine the target analyte. Antibodies, enzymes, cells, aptamers, DNA or RNA, all are examples of bioreceptors [27]. Conversely, transducers are devices that, when exposed to chemical/biological targets, convert energy from one form to another and produce a measured signal. Lastly, the data is amplified, processed, and prepared for display using amplifiers [4]. Based on the parts of biosensors such as bioreceptors and transducers or based on technology, biosensors are distributed into various categories as shown in Fig. 2. On the basis of receptors, biosensors are classified into antibodies, aptamers, enzymes, and whole cells. The other classification is based on technology, and biosensors are categorized as electrometers, nano-biosensors, biosensor chips, and SPR (surface plasma resonance). But in this work, the major focus has been given to classification based on transducers and, more specifically, electronic transducers, which has been discussed in detail in further sections.

2.1. Classification based on transducers

Biosensors can be classified based on the operating principle of the transducer devices used into categories, namely electrochemical, optical, electronic, thermal, and acoustic. The working principle behind the electrochemical biosensors is that ions or electrons are produced or consumed during chemical reactions between the target analyte and immobilized biomolecule. These events impact the solution's measurable properties, such as potential or electric current [28]. Electrochemical biosensors can further be classified based on the transduction principle as potentiometric, amperometric, impedimetric, conductometric, and voltametric [4]. Optical biosensors are based on the principle of optical diffraction and they work by detecting luminescent, fluorescent, colorimetric, or other optical signals that result from microbes interacting with analytes. These biosensors can link the concentration of target chemicals with the observed optical signal [29]. The other class is of electronic transducers whose working largely depends on FETs and they can interpret the interactions between the FET surface and analyte directly [30]. Thermal biosensors determine the change in energy in the surroundings of a system. These biosensors are built by immobilizing biological elements onto temperature sensors, allowing for the determination of the energy shift sourced by bio-recognition between a system and its environment [31]. Acoustic biosensors operate by altering the physical characteristics of acoustic waves when there is a variation in the quantity of analyte absorbed. Commonly utilized material for fabricating sensor transducers is piezoelectric materials as they have the ability to generate and propagate frequency-dependent acoustic waves [32].

2.2. Limitations of existing technologies

A plethora of research has been conducted on the application of biosensors in laboratories, but the commercialization of biosensor devices is still primarily unattainable, as these devices have a lot of strengths but have a few weaknesses, like this (Fig. 3A). Among the few successful commercial applications so far, glucose sensors stand out [33]. The discrepancy between research results and real-world applications might be ascribed to the difficulties in attaining large-scale integration and simple fabrication of up-scaled miniaturized devices, and scaling of biosensing devices requires integration, and the key requisites of electrical devices are shown in Fig. 3B. [34]. In laboratory settings, a variety of biosensors with varying technologies such as optical, electronic, and electrochemical transducers have shown encouraging results in terms of sensitivity and selectivity [35–37]. However, among these, biosensors employing electronic transducers possess the potential to bridge this gap. Leveraging FET technology, these biosensors hold promise for miniaturization, particularly with the utilization of different FET-based device architectures [38]. This advancement is crucial in making biosensor devices portable and user-friendly, thus opening the door for commercial applications [39].

3. FET-based devices compatible with CMOS processes for biosensor miniaturization

Recently, FET-based biosensors have garnered significant interest among researchers because of features, such as label-free detection, compact size, rapid response time, reliability, and integration with CMOS processes enabling miniaturization. These sensors offer the potential for on-chip integration of amplification circuitry and sensors, enabling mass production at low cost. Additionally, they provide high selectivity and reusability, further enhancing their appeal for various

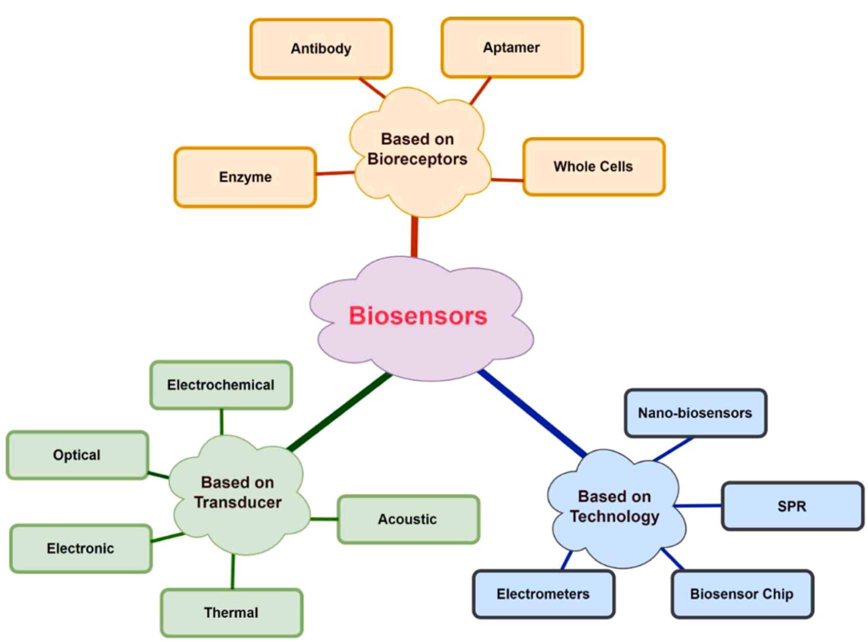

Fig. 2. Schematic presenting different type of biosensing system.

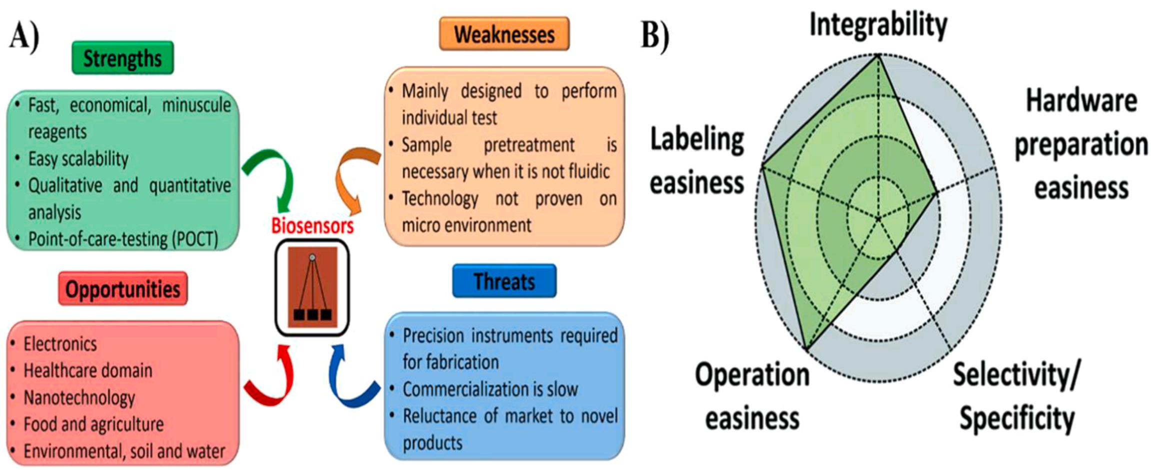

Fig. 3. A) SWOT analysis of Biosensing technology (reproduced with permission from [40] [distributed under Creative Commons Attribution 4.0 International]) and B) Radar chart, demonstrating the required characteristics of Electrical transducing mechanism (reproduced with permission from [41] [distributed under Creative Commons Attribution 3.0 Unported Licence]).

applications. This section deals with various FET-based biosensor devices (Fig. 4), their role in biosensor miniaturization along with their working principle and compatibility with CMOS processes has been discussed.

3.1. MOSFET (Metal oxide semiconductor FET)

The MOSFET is a versatile type of transistor utilized in a wide range of electronic circuits, including biosensing units. One of the defining features of MOSFETs is their metal oxide gate electrode. This gate is insulated by an ultra-thin layer of insulating material, typically SiO_2, which separates it from the main channel positioned between the drain and the source. This insulator results in the MOSFET having an exceptionally high input resistance [42,43]. The electrical conductivity of the MOSFET is determined by the voltage applied to the gate electrode. This change in conductivity in response to the applied voltage makes MOSFETs suitable for amplifying or switching electronic signals [42]. MOSFETs are particularly promising candidates for biosensors due to their capability to directly convert bio-interactions into readable signals [44]. In biosensing applications, MOSFET-based sensors operate in the sub-threshold region to achieve maximum sensitivity. This sub-threshold operation allows for highly sensitive detection of bio-interactions, making MOSFETs well-suited for a variety of sensing applications [45,46]. To date, several works have been reported utilising MOSFETs in biosensor applications. A biosensing device based on MOSFET for the recognition of C-reactive protein (CRP) was reported and this device sensed the binding of CRP to a specific antibody by quantifying the drain current of the MOSFET [47]. Further, to improve the performance and utilization, various gate structures can be used in MOSFET-based biosensor device development. Deepak Singh et al. [48] have reported a detailed comparative analysis of conventional back-gate and three front-gate structures and studied them in terms of sensitivity and electrical parameters. From the findings of this study, it was revealed that the electrical parameter is influenced solely by the biomolecules, and negative charge density in the back-gate structure. This limitation restricts its ability to detect neutral biomolecules. On the other hand, electrical parameters are affected by two different factors i.e. the dielectric permittivity and negative charge density in the front-gate-based structures. As a result, biosensor structures based on front-gate demonstrate the capability to detect both neutral and charged biomolecules. Moreover, to improve the current response of MOSFET, a hybrid biosensor using the conventional CMOS technology offers the advantage of high density and low noise performance. Jieun Lee at al. [49] reported a Silver Nanowire (SiNW) based MOSFET hybrid biosensor. In this work, SiNW plays the role of a sensor and MOSFET acts as a transducer. The SiNW and MOSFET are monolithically integrated and connected via conventional CMOS technology. The resulting device, owing to its compatibility with conventional top-down CMOS processing technology, has its application in the biomedical domain where it can help in the formation of miniaturized devices.

3.2. ISFET (Ion-sensitive FET)

ISFETs are used for bio-sensing applications, by demonstrating a linear relationship between obtained source-drain current and ion concentration. In 1970, the first ISFET was proposed by Bergveld with Na^+ sensitivity [50]. ISFET structure is similar to that of MOSFETs, except that the metal gate is replaced by a reference electrode or sensitive membrane deposited on top of the gate, which is used to provide bias voltage (V_{gs}) in an ISFET. Thus, the gate potential generated at the interface between the solution and the sensitive membrane controls the flow of source-drain current. ISFETs are one of the successions of MOSFETs that enable CMOS-based biosensing [51].

The integration of ISFETs and CMOS technology requires modification in the structure of ISFETs. In this regard, Bousse et al. [52], fabricated ISFET devices with an electrically-floating polysilicon gate in accordance with the CMOS process. Further, Bausells et al. in 1999 [53], demonstrated the ISFETs fabrication in an unmodified CMOS process where the gate of ISFET is extended to the passivation layer on top. Since then, many modifications on structures and use of nanomaterials such as SiNW [54] or Carbon nanotube (CNT) [55] have been done to enhance compatibility with standard CMOS processes, device scalability, and large integration density. Georgiou et al. [56] suggested utilizing a commercial 0.25 µm CMOS technology to create an ISFET-based pH sensor. Gubanova et al. proposed a CMOS compatible novel ISFET structure that uses hafnium oxide-coated aluminium pad surface as a floating/extended gate. Further, this ISFET was combined with tyrosinase enzyme to develop a biosensor for detection of phenols. With their work, they stated that CMOS-compatible ISFETs have benefits such as small size, low cost and mass production, making them a suitable candidate for point-of-care detection [57]. Integrating the ISFET sensing array into conventional CMOS technology not only enhances its sensitivity and scalability but also simplifies compatibility and calibration. This integration opens the door to creating a bio-sensing system-on-chip (SoC) platform by incorporating the readout circuitry and memory within the current VLSI technology framework [42].

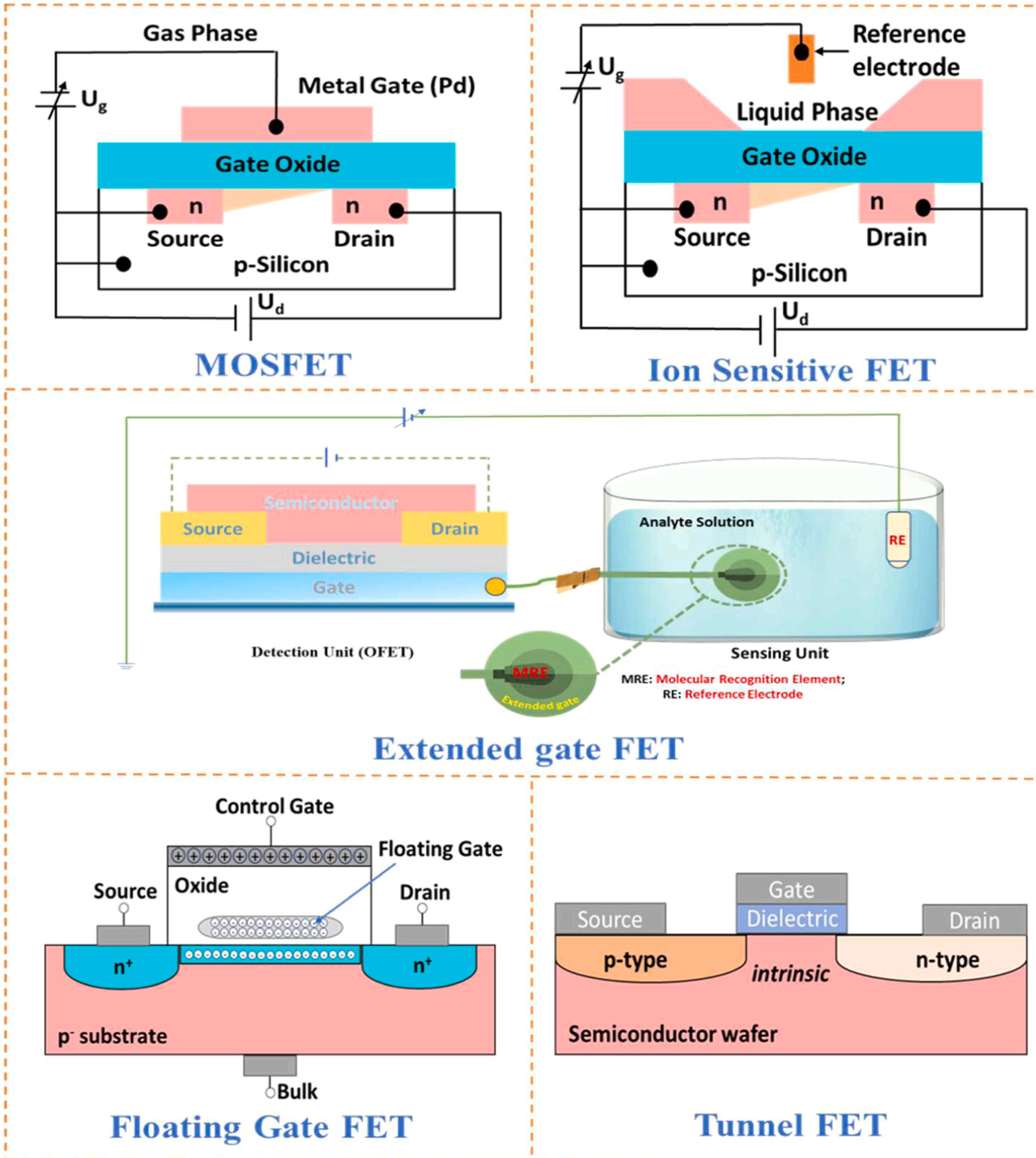

Fig. 4. Various architecture of FET technology.

3.3. FGFET (Floating gate FET)

A FGFET is a derivative of ISFET and its structure incorporates two gates: the sensing gate and the control gate. The sensing gate transforms chemical signals from analytes into electrical signals, while the control gate supplies bias to the FET. This configuration allows the control gate to provide the necessary bias, potentially eliminating the need for a separate reference electrode [42,58]. Barbaro et al. [59] demonstrated the first FGFET. This FET architecture is used in various biosensing and bioelectronic applications such as pH, and enzyme sensing, among others. An FGFET for pH sensing and enzymatic reaction detection was demonstrated by Zhang et al. [60]. To provide robust, long-term recordings, the sensor physically protects the transistor channel from the electrolyte and is also compatible with CMOS technology [61]. Meyburg et al. presented the integration of the CMOS process with FGFET technology as sensor input for bioelectronics applications. They fabricated an array of 32 × 32 FGFET and employed CMOS processes for the implementation of simple integrated chips [62].

3.4. EGFET (Extended gate FET)

A derivation of the ISFET design, the extended-gate field-effect transistor (EGFET) was first conceptualized in 1983 by J. Van Der Spiegel and associates [63]. MOSFET's metal gate is replaced in the standard ISFET arrangement by an ion-sensing film, an electrolyte solution, and a reference electrode. Conversely, the EGFET preserves the conventional MOSFET architecture while extending the gate to establish connections with the reference electrode, electrolyte solution, and metal-sensing layer [64]. The EGFET includes a number of characteristics, including a disposable sensor head, ease of packing, resistance to light and temperature changes, and easily replaceable sensor film. Moreover, to enhance the selectivity of the fabricated sensor, the gates of the EGFETs can be integrated with MIPs, as they have molecularly imprinted cavities with recognition sites. Due to this property MIPs are utilised for selective detection of small molecules and macromolecular compounds [65]. Liu et al. presented a MIP-based EGFET sensing system which is used for measurement of C-reactive protein (CRP) concentration in human serum [66]. Compared to ISFETs, EGFET has better thermal and chemical stability as well as increased current sensitivity. EGFETs are used for the detection of pH, enzymes, and proteins [67]. Pan et al. proposed an approach to fabricate solid-state EGFET pH sensor using Ti/Ni sensitive membranes on n^+ type Si substrate [68]. Signal-to-noise ratio (SNR) can become the system of measurement to analyze the performance of an EGFET in terms of factors, namely transconductance (g_m), oxide traps, and device dimensions. Rajan et al. observed a linear dependency between SNR and $\sqrt{WL}$ and hence proved that EGFETs with the high surface area are better for a lower limit of detection and enhanced sensitivity [69]. Very few works have been reported in the area of scaling down of EGFET devices or in the direction of their integration with current CMOS technology. Kuo et al. utilized 0.18 μm CMOS technology (Fig. 5A) to design the EGFET sensing window and the MOSFET device on a single chip [70]. Six metal layers (Fig. 5B) comprised the detection window. To detect lactic acid (LA), ruthenium dioxide (RuO_2) film was functionalized with lactase and sputtered over the surface. With the integration of MIP with EGFETs we can enhance the stability and selectivity of the sensor system without compromising on the cost. Moreover, MIP based sensing systems can be developed into lab-on-chip technology after integration with electronics and microfluidics. But there is still a lot of research gap in single-chip detection using EGFET technology.

3.5. Carbon-based FET

As power consumption and chip size shrink in the electronics industry, new strategies are sought to achieve optimal performance. Materials like carbon nanotubes (CNTs), graphene, fullerenes, and carbon dots (CDs) are being explored due to their exceptional electrical and thermal properties, especially in FET-based architectures [71]. The development of carbon nanotube field-effect transistors (CNTFETs) stemmed from the goal of minimizing or eliminating short-channel effects while enhancing transistor performance at these scales [72]. Semiconducting CNTs are preferred over metallic nanotubes due to their ability to be fully switched off. These transistors offer several advantages, including higher current density, ballistic electron transport along their lengths [73], low power consumption compared to silicon counterparts, and fast operational speed [74]. The emergence of field-effect transistors known as GFETs is only possible due to the discovery of graphene with unique electronic characteristics, which offer it variety of

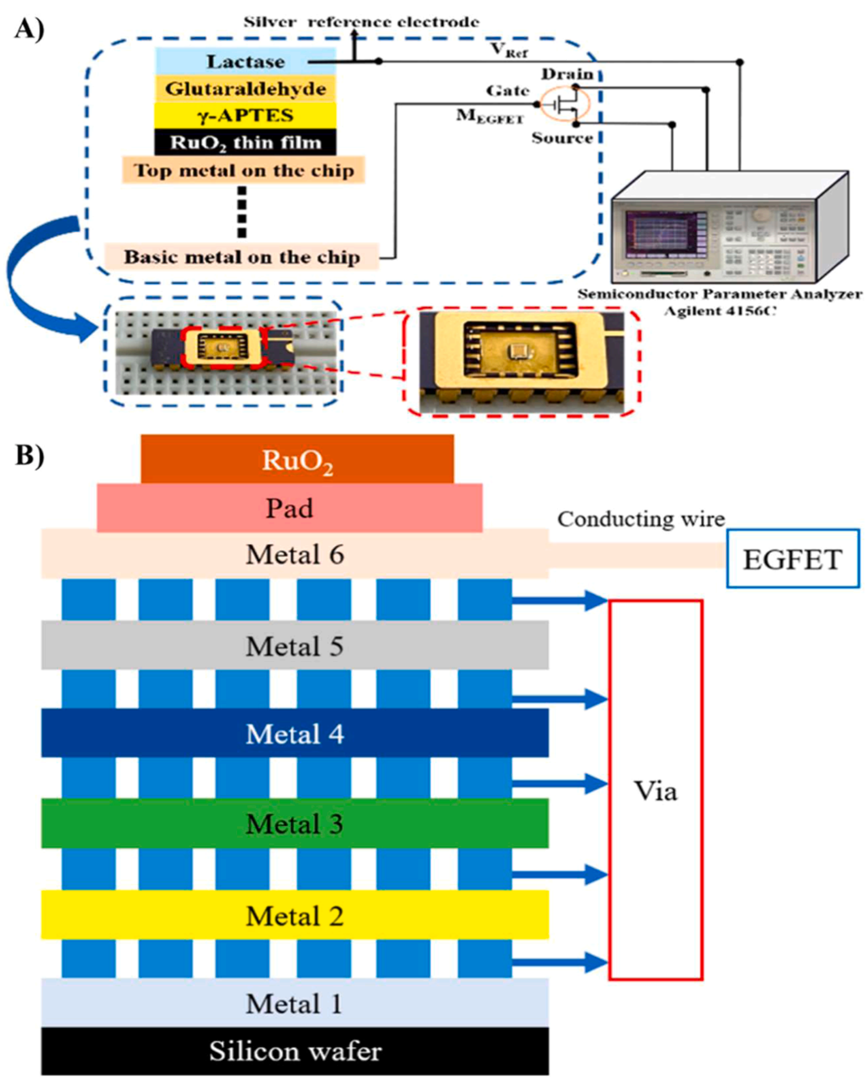

Fig. 5. A) Measurement setup of fabricated CMOS technology & B) Architecture of using six metal layers for MOSFET device fabrication (reproduced with permission from [70]).

applications as an active material for developing electronic devices. GFETs utilize graphene for ballistic carrier transport. CNT-based FETs demonstrate the ability to achieve great on-off ratio (>10^5), high gain (>10), and an ability to operate at room temperature [75]. Gas sensors and biosensors fabricated from one-dimensional nanostructures are particularly appealing due to their unique performance in terms of higher sensitivity and quick response to the exposed analyte in the surrounding environment and this is owing to the fact that one-dimensional nanostructures have large surface-to-volume ratio and reduced dimensions [76,77]. A p-type CNT-FET approach has been used for the swift detection of the surface spike protein S1 of SARS-CoV-2. This method employs CNTs as charge-transfer transducers and relies on anti-SARS-CoV-2 S1 antibodies for protein selectivity [78]. In response to the COVID-19 pandemic, G-FET biosensors with surface-decorated AuNPs have been developed. These sensors exhibit high sensitivity to trace amounts of the RdRp gene using uncharged complementary oligomeric probes, PMO, immobilized on the AuNP surface [79].

Carbon-based FETs have laid the foundation for system-on-chip biosensors utilizing CMOS-based circuits. Lee et al. developed a biosensor system-on-a-chip (SoC) based on CNT for detecting neurotransmitters [80]. This system integrated 64 CNT-based sensors with silicon-based signal processing circuits on a single chip, enabling the detection of glutamate, a neurotransmitter. Ammonia, a byproduct of the enzymatic reaction between glutamate and glutamate oxidase on CNT-based sensors, modulated the conductance signals to the CNT-based sensors. Additionally, Dudina et al. introduced a monolithic biosensor platform based on CNTFETs for detecting the neurotransmitter glutamate [81]. They utilized an array of 9 × 216 CNTFET devices with 96 integrated readout and amplification channels, all realized in CMOS technology.

3.6. TFET (Tunnel FET)

The structure of TFET comprises three regions namely source, drain and channel. In TFET, different doping is done for both source and drain, unlike other conventional FETs. The TFET structure is similar to that of a p-i-n diode with a gate. Moreover, the barrier width is kept thin to facilitate the tunneling of charge carriers [82]. The scaling down of MOS devices, as per Moore's law, has some limitations like increased gate-oxide leakage, short channel effects like drain-induced barrier lowering (DIBL), and lowering of threshold voltage [83,84]. TFETs have proven to solve the above limitations and are suitable for low-power VLSI applications. The mode of conduction of charge carriers in TFETs follows thermionic emission phenomenon owing to the unique property of band-to-band tunneling, thereby reducing power consumption [85]. Trivedi et al. discussed the application of TFETs in low-power cellular neural network (CNN) based associative memory (AM) owing to the lower OFF current (I_{off}) and subthreshold swing (SS) in TFETs [86]. These characteristics make them potential candidates for low power consuming static random-access memory (SRAM) cells [87].

There are a few limitations of conventional TFET devices such as ambipolar conduction which results in conduction in opposite directions when the device is in OFF state and lower ON current (I_{on}). To solve this, asymmetrical doping for source and drain utilizing different structures or other modifications is proposed [85]. Reddy and Panda proposed a TFET structure with overlapped gate-on-drain gate all around TFET (GAA-TFET) biosensor which showed enhanced sensitivity and lower leakage current [88]. The use of modern nanomaterials like CNT, SiNW have also proved beneficial in improving the efficiency of TFET devices. A novel biosensor based on CMOS-compatible SiNW-TFET was proposed by Gao et al., where he demonstrated anti-interference capability by applying inherent ambipolarity [89]. Thus, compatibility with CMOS technology, ease of scaling down and low power operations have provided TFETs with a variety of applications in modern chip-based technologies such as IoT, Artificial Intelligence (AI), among many [90,91].

4. Surface chemistry for CMOS and MIP biosensors

Surface chemistry plays an integral role in enhancing the performance of biosensors, as it governs the interaction between the sensing element and the target analyte. The development of robust and precise surface chemistries is particularly critical for integrating MIPs and CMOS-based systems, both of which have emerged as promising avenues for biosensor technologies. MIPs are synthetic recognition elements designed to mimic the binding sites of target molecules. Their synthesis begins with a pre-polymerization process involving the target molecule (template) and functional monomers, stabilized by non-covalent forces like hydrogen bonding, Van der Waals interactions, and π–π stacking [92]. Cross-linkers are introduced to form a rigid polymer matrix around the template, and subsequent removal of the template leaves imprinted cavities specific to the target molecule. The chemical and physical properties of the polymer can be fine-tuned by varying the cross-linker concentration and the choice of monomers [93]. Surface functionalization of MIPs is key to their integration into biosensing platforms. For instance, incorporating organic or inorganic ligands can enhance the specificity and sensitivity of the MIP layer. Metallic or covalent bonding with functional groups on the polymer matrix facilitates strong and stable attachment to the sensor substrate [94]. Self-assembly processes using metallic or π-interactions are also employed to ensure uniform deposition and stability of the MIP layer [95]. These approaches enable MIPs to function effectively in diverse sensing modalities, including electrochemical and optical systems.

CMOS-based biosensors leverage the integration of electronic circuitry with biological or synthetic recognition elements, enabling high-throughput, scalable, and cost-effective diagnostic platforms. However, challenges like surface oxidation, porosity, and material incompatibility can limit the efficiency of CMOS-based systems. Oxidation of CMOS surfaces, such as aluminum pads, can create irregular oxide layers that compromise the sensing performance. Stabilization techniques, such as the deposition of controlled thin oxide layers (e.g., SiO_2 or Al_2O_3), ensure consistent thickness and quality. These layers provide a stable dielectric interface for biochemical interactions [96]. Functionalizing CMOS surfaces with self-assembled monolayers (SAMs) or polymeric coatings improves biocompatibility and minimizes nonspecific interactions. SAMs are particularly useful for tailoring surface hydrophobicity and charge properties, which influence analyte binding and signal transduction. Additionally, the incorporation of nanomaterials such as gold nanoparticles (AuNPs) or graphene enhances signal amplification and binding efficiency. These materials act as mediators between the CMOS substrate and the biochemical interface, enabling more sensitive detection.

The combination of MIPs with CMOS technology offers a unique advantage for biosensor applications. MIPs provide high selectivity and stability, while CMOS ensures miniaturization and integration with electronic systems. Uniform deposition of MIP layers onto CMOS electrodes using spin-coating or dip-coating methods ensures consistent performance. Optimizing the polymer thickness is critical to maintaining both the sensitivity of the CMOS device and the specificity of the MIP layer [97,98]. Functionalization with conductive polymers or metallic layers enhances the electron transfer between the MIP and the CMOS substrate, which is particularly important for electrochemical biosensors where signal amplification is directly linked to interface conductivity [99]. Applications of MIP-CMOS integrated systems highlight the advantages of this synergy. Electrochemical sensors employing MIPs have demonstrated exceptional sensitivity and stability, with applications ranging from environmental monitoring to clinical diagnostics. Optical fiber sensors integrated with CMOS-compatible MIPs have achieved high specificity in detecting complex analytes, while advanced CMOS designs incorporating MIP-modified microelectrodes have enabled point-of-care diagnostics. These examples underscore the pivotal role of surface chemistry in enhancing the functionality and reliability of biosensors, particularly in applications demanding high precision and integration.

5. Advanced biosensing systems integrated with IoT

Advancements in fabrication technology have miniaturized semiconductor devices, enabling compact, powerful, and affordable systems. This scalability facilitates field-deployable IoT applications, particularly enhancing wearable biosensing devices, making them more accessible and effective than ever before. Wearable biosensing devices have gained a lot of attention these days due to their potential to revolutionize healthcare by enabling point-of-care diagnostics and treatment [100]. The integration of Internet of Things (IoT) technology further enhances the capabilities of these devices by facilitating seamless data transmission and analysis, thereby enabling remote monitoring and personalized healthcare solutions. These integration of IoT technology into wearable biosensor devices is made possible by nanotechnological advancements, as one of the crucial aspects in miniaturization and fabrication of IoT-integrated biosensors are incorporation of nanomaterials [7,101]. Nanotechnology offers several advantages such as increased sensitivity, selectivity, and stability to the biosensors, making them more efficient for detecting biomolecules like glucose, proteins, and DNA. Moreover, IoT helps in connecting these nano-integrated biosensors to the internet, enabling data collection, analysis, and sharing in real-time. Through IoT connectivity, healthcare professionals can remotely monitor patients' health status, track disease progression, and intervene promptly when necessary. This real-time monitoring capability has the potential to improve patient outcomes, especially for individuals with chronic conditions. Major challenges in the development and implementation of nano-integrated wearable biosensor devices, include ensuring device biocompatibility, stability, and reliability, as well as addressing privacy and security concerns [7,102]. Thus, the current need of the hour is standardization and regulatory frameworks to ensure the safety and effectiveness of these devices. Hence, integration of IoT technology into nano-integrated wearable biosensor devices (Fig. 6A) holds immense promise for healthcare applications, apart from this it also can be utilized for environmental and agricultural applications. By enabling continuous monitoring, real-time data analysis, and remote connectivity, these devices have the potential to revolutionize the healthcare system and reduce healthcare costs; in addition, the mechanism for fabricating these IoT-integrated sensors is presented in Fig. 6B. However, addressing technical challenges and regulatory hurdles will be crucial for realizing the full potential of this technology in the future.

6. Challenges and future directions

Electronics have revolutionized the field of biosensing for various applications, namely healthcare, environmental monitoring, and food safety, by offering high sensitivity and specificity. Despite their immense potential, electronic biosensors face several challenges, including integration, cost implications, accessibility issues, and technological limitations. Integration challenges in electronic biosensors arise at the time of seamlessly merging multiple sensing units and signal processing components on a single platform [103,104]. For achieving this, it requires innovative approaches in microfabrication, system design, and integration techniques, which will further help in maintaining performance, reliability, and cost-effectiveness [105]. The current need of the hour is to overcome these challenges to develop a portable and

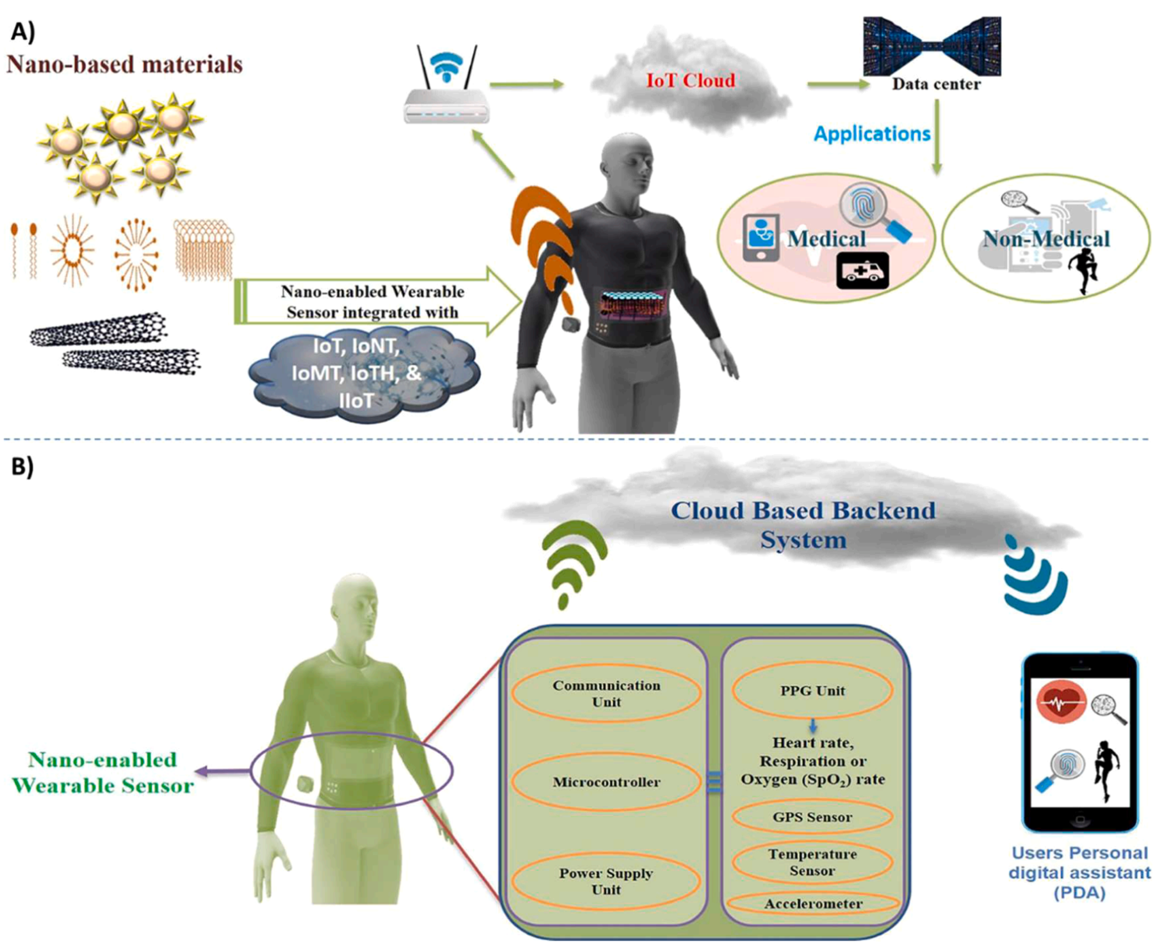

Fig. 6. A) Advancement in IoT based sensors; B) Mechanistic framework of the IoT-based sensor (reproduced with permission from [8]).

user-friendly biosensing system that has diverse applications, ranging from point-of-care diagnostics to environmental monitoring. Further, cost-effectiveness is one of the primary challenges associated with electronic biosensors. As higher cost of production often limits widespread adoption of any product, especially in resource-constrained settings. Additionally, professional expertise and specialized equipment's are required for the fabrication of sophisticated biosensing system, that contributes majorly to the overall expense [106]. Thus, the cost factor is significant barrier in accessibility of electronic biosensors, and this is majorly observed in the developing countries where financial resources are limited. Moreover, its accessibility is also hindered by its complex operation and interpretation of results that is not easily understandable by layman and requires skilled professional for operation and data analysis. So, several existing biosensing platforms cannot be deployed in decentralized or point-of-care settings [107]. These challenges can be avoided by simplifying the user interface and enhancing the portability of these devices, which will enable their accessibility, particularly in resource-limited environments.

In addition, various biosensor technologies, each with unique benefits and drawbacks, are commercially accessible, for example, enzyme-based electrochemical biosensors' high sensitivity and specificity make them appropriate for various uses, such as glucose management and diabetes treatment [108]. Although shelf life and unstable enzymes cause severe problems with their long-term dependability. However, surface plasmon resonance (SPR) biosensors provide label-free detection and real-time monitoring, making them useful instruments for drug discovery and research on biomolecular interactions [109]. But SPR equipment sophistication and the need for exact alignment prevent them from being widely used outside research labs. Current electronic biosensors have potential, but several issues prevent them from being widely used. The challenges include low selectivity, limited sensitivity, and vulnerability to environmental interferents [110]. Moreover, integrating several sensing units into a single platform is still a difficult challenge; thus, creative solutions are needed to overcome these constraints. Advancements in the electronic field, notably in complementary metal-oxide-semiconductor (CMOS) and very-large-scale integration (VLSI) technologies, hold promise for overcoming these drawbacks of electronic biosensors.

Miniaturization of biosensing components and signal processing circuitry enables fabrication of compact and integrated biosensing system that demonstrates enhanced performance and reduced power consumption [104]. To further achieve miniaturization of the biosensing system, integration of on-chip microfluidics enables ease of sample handling and analysis, thereby streamlining the entire procedure and enhancing repeatability [103]. Hence, electronic biosensors are powerful tool for real-time monitoring and detection of biological analytes of interest. However, challenges related to integration, cost, accessibility, and technological limitations hinder their widespread consumer adoption. While commercial biosensors have many benefits, they also have inherent drawbacks and need of hour is to overcome these challenges. Thus, it requires great efforts in advancing electronic components, compatible with CMOS technology, that will further enable the development of next-generation biosensing platforms with improved performance, portability, affordability, selectivity, and sensitivity.

7. Conclusion and prospects

This comprehensive review delves into the intricate landscape of biosensing technology, emphasizing its pivotal role in sustainable development across various sectors. It elucidates the foundational principles of biosensing, emphasizing the symbiotic relationship between electronic devices and transducers. By exploring diverse applications spanning healthcare, environmental monitoring, and industrial processes, it highlights the profound impact of biosensors on achieving the United Nations Sustainable Development Goals. Moreover, the integration of biosensors with CMOS technology and IoT presents a promising avenue for enhancing real-world efficacy, scalability, and accessibility. Despite the challenges of integration, cost, and accessibility, ongoing innovations in electronic biosensing offer a pathway toward overcoming these hurdles. By leveraging advancements in FET architectures compatible with CMOS technology, the future promises more compact, portable, and user-friendly biosensing devices, capable of addressing critical societal needs. One important factor for achieving FET architecture-compatible CMOS technology for sensing applications is utilizing label-free sensing, which typically lacks selectivity and specificity. However, incorporating molecularly imprinted polymers (MIPs) can effectively address these challenges. MIPs provide a robust solution by mimicking the binding sites of specific target molecules, thus enhancing the sensor's selectivity and specificity. Additionally, the use of MIPs reduces the need for bio-receptor immobilization on the device, facilitating seamless integration with CMOS technology. This approach not only simplifies the manufacturing process but also ensures that the sensor retains its selectivity, sensitivity, and overall sensing properties, making it highly suitable for various practical applications in the field of biosensing. Furthermore, MIPs offer stability and reusability, which are crucial for developing cost-effective and reliable sensing systems. Ultimately, this review underscores the transformative potential of electronic biosensors in advancing sustainable development and fostering a path toward a more interconnected and resilient future.

CRediT authorship contribution statement

Harshita Rai: Writing – original draft, Visualization, Investigation, Conceptualization. **Kshitij RB Singh:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization. **Arunadevi Natarajan:** Writing – original draft, Investigation. **Shyam S. Pandey:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

Data availability

No data was used for the research described in the article.

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