Fusion of Multidisciplinary Research, An International Journal (FMR) , Vol.**5**, Iss.**2**, 2024
https://doi.org/10.63995/KXWE9651

ARTICLE

The Revolutionary repercussion of Cell Sensor Technology in Live-cell Biosensors

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(Received: 23 February 2024; Revised: 27 April 2024; Accepted: 19 May 2024; Published: 01 July 2024)

Abstract

Cell sensor technology has transformed the landscape of biological sensing by enabling real-time monitoring of cellular processes with unprecedented precision and sensitivity. This article explores the underlying principles of cell sensor technology, highlighting its integration with live-cell biosensors to detect and measure physiological and biochemical changes within living cells. The study examines various applications of live-cell biosensors, including disease diagnosis, drug discovery, environmental monitoring, and personalized medicine. By providing continuous and dynamic data, these biosensors offer significant advantages over traditional static assays, allowing for more accurate and timely decision-making in clinical and research settings. Additionally, the article addresses the advancements in sensor design, such as the use of nanotechnology, fluorescence-based sensors, and microelectromechanical systems (MEMS), which enhance the functionality and scalability of live-cell biosensors. The article also discusses the challenges and future directions in this rapidly evolving field, such as improving sensor stability, ensuring biocompatibility, and integrating artificial intelligence for data analysis. By synthesizing current research and technological innovations, this article underscores the transformative potential of cell sensor technology in advancing the capabilities and applications of live-cell biosensors.

Keywords: Biocompatibility; Cell sensor technology; Disease diagnosis; Live-cell biosensors; Nanotechnology; Personalized medicine; Real-time monitoring; Sensor design

Abbreviations: CNC: Computer Numerical Control, ELF: Extremely low frequency, ECIS: Electric Cell–Substrate Impedance Sensing, FET: Field-effect Transistor, FRET: Fluorescence resonance energy transfer, GFPP: Green fluorescent protein, POP: Persistent organic pollutants, SAM: Self-Assembled Monolayers, SPR: Surface plasmon resonance, MEMS: Microelectromechanical Systems, MIP: Molecularly Imprinted Polymers

1. Introduction

Cell sensor technology has revolutionized the field of live-cell biosensors, enabling the development of advanced sensing platforms that interface molecular machinery with microelectronics. Biosensors have wide-ranging applications in drug discovery, biomedicine, environmental monitoring, and national security, emerging as next-generation detection tools that combine chemistry, physics, and biology [1, 2, 3, 4]. This article explores the principles and design of live-cell biosensors and the role of cell sensor technology in transducing and detecting signals. It examines applications in environmental monitoring, such as radiation detectors for electromagnetic fields and extremely low frequency (ELF) electromagnetic radiation, as well as biomedical uses for disease diagnosis and treatment. Additionally, it delves into challenges, limitations, recent advancements, and future directions for this revolutionary technology (Fig. 1) [5, 6, 7, 8].

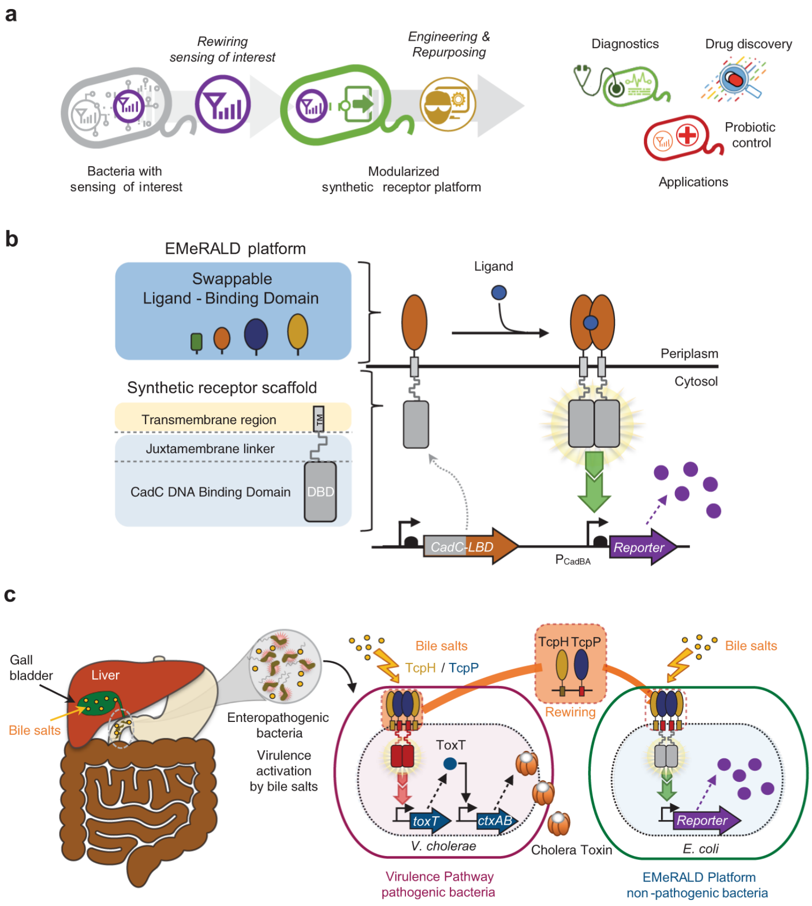

Figure 1. Design principles and architecture of EMeRALD-based bacterial sensors

In the rapidly advancing field of biotechnology, the development and application of cell sensor technology have ushered in a new era of precision and innovation. Live-cell biosensors, which utilize living cells to monitor and report on their immediate environment, represent a significant breakthrough in biological sensing. This technology has transformed our ability to observe and measure physiological and biochemical changes within living cells in real-time, offering unprecedented insights into cellular processes and enabling a wide array of applications in medical diagnostics, drug discovery, environmental monitoring, and personalized medicine. Cell sensor technology integrates the principles of cellular biology with sophisticated engineering to create devices that can detect and respond to specific biological signals. These biosensors leverage the natural abilities of cells to sense and react to their surroundings, providing a dynamic and continuous flow of information that static assays cannot match. This ability to monitor cellular responses in real-time has profound implications for understanding complex biological systems and developing new therapeutic strategies [9, 10, 11, 12, 13, 14, 15].

One of the most significant advantages of live-cell biosensors is their capacity for real-time monitoring. Traditional methods of biological analysis often involve destructive sampling and endpoint measurements, which can miss the dynamic changes occurring within cells. Live-cell biosensors, on the other hand, offer continuous observation, capturing the temporal aspects of cellular responses and providing a more comprehensive understanding of biological phenomena. This real-time capability is particularly valuable in applications such as drug discovery, where the effects of potential therapeutics on cellular behavior can be monitored continuously, leading to more accurate and timely evaluations. The integration of advanced technologies such as nanotechnology, fluorescence-based sensors, and microelectromechanical systems (MEMS) has further enhanced the functionality and scalability of live-cell biosensors. Nanotechnology, for example, allows for the development of sensors at a molecular scale, increasing sensitivity and enabling the detection of minute changes in cellular environments. Fluorescence-based sensors utilize the principles of fluorescence to provide visual readouts of cellular activity, facilitating easier interpretation and analysis. MEMS technology, which involves the fabrication of tiny mechanical devices, has enabled the creation of highly precise and portable biosensors that can be used in a variety of settings [16, 17, 18, 19].

Despite the remarkable advancements, the field of live-cell biosensors faces several challenges that need to be addressed to fully realize its potential. One of the primary challenges is ensuring the stability and longevity of the sensors. Living cells are inherently complex and can be sensitive to external conditions, which can affect the reliability and consistency of the biosensors. Additionally, ensuring biocompatibility—making sure that the sensors do not adversely affect the cells or their environment—is crucial for accurate and meaningful data collection. Another challenge lies in the integration of artificial intelligence and machine learning techniques to analyze the vast amounts of data generated by these biosensors. Advanced data analytics can help in identifying patterns and making predictions, thereby enhancing the utility of live-cell biosensors (Fig. 2) [20, 21, 22, 23, 24].

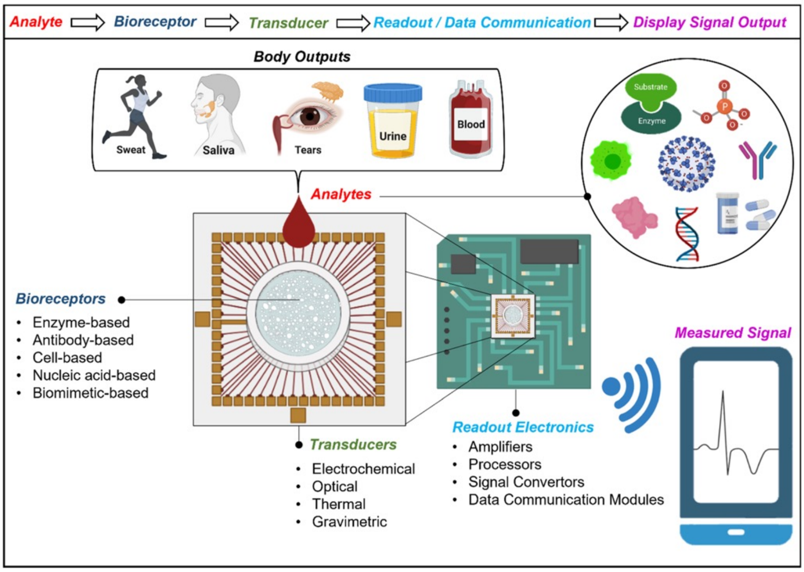

Figure 2. Schematic illustration of biosensing.

In this research article, we explore the revolutionary impact of cell sensor technology on the development and application of live-cell biosensors. We examine the underlying principles and recent advancements in sensor design, highlighting the transformative potential of this technology in various fields. Through a comprehensive analysis of current applications and future directions, this article aims to provide a detailed understanding of how cell sensor technology is revolutionizing biological sensing and paving the way for new scientific and medical breakthroughs. The synthesis of current research and technological innovations underscores the importance of continued investment and exploration in this promising area of biotechnology [25, 26, 27].

2. Types of Live-Cell Biosensors

Live-cell biosensors are an essential tool in modern biotechnology, enabling real-time monitoring of cellular processes. These biosensors can be classified into several types based on their design and detection mechanisms. Each type offers unique advantages and is suited for specific applications [28, 29, 30].

1. **Fluorescence-based Biosensors:** Fluorescence-based biosensors utilize fluorescent proteins or dyes to monitor cellular activities. These biosensors can detect changes in cellular environment, such as pH shifts, ion concentrations, or the presence of specific biomolecules. For example, the green fluorescent protein (GFP) can be genetically encoded into cells to report on the expression levels of target proteins. Fluorescence resonance energy transfer (FRET) is another technique used to monitor molecular interactions within living cells, providing insights into protein-protein interactions and other dynamic processes (Fig. 3) [31, 32, 33].

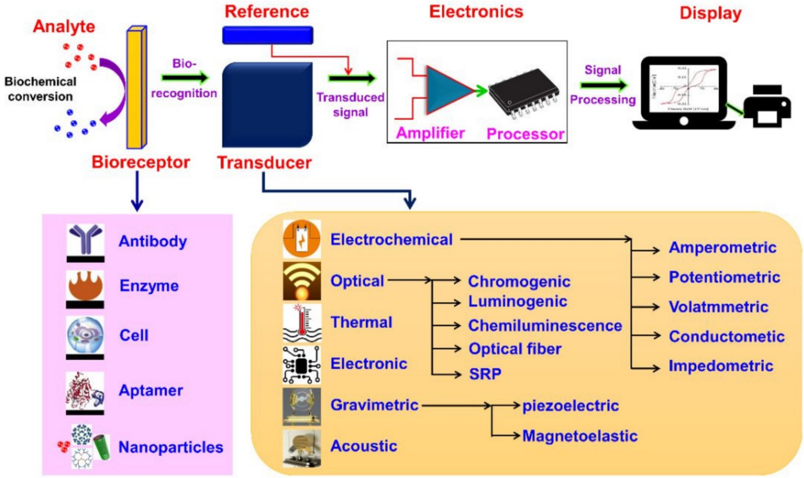

Figure 3. Biosensors and their components.

2. **lectrochemical Biosensors:** Electrochemical biosensors measure the electrical signals produced by biochemical reactions within cells. These biosensors typically involve electrodes that interact with cellular components to detect changes in redox states, ion fluxes, or other electrochemical properties. Electrochemical biosensors are particularly useful for detecting small molecules, such as glucose or neurotransmitters, making them valuable in medical diagnostics and neurobiology research.
3. **Optical Biosensors:** Optical biosensors employ various light-based techniques, such as absorbance, reflectance, or surface plasmon resonance (SPR), to detect changes in cellular behavior. These biosensors can monitor cell growth, adhesion, and morphological changes. SPR-based biosensors, for instance, are highly sensitive and can detect minute changes in the refractive index near the cell surface, providing valuable information about cellular interactions and dynamics.
4. **Mechanical Biosensors:** Mechanical biosensors, such as those utilizing microelectromechanical systems (MEMS), detect physical changes in cells, including mechanical stress, deformation, and cellular motion. These biosensors are used to study cell mechanics, which is crucial for understanding processes like cell migration, division, and differentiation. MEMS-based biosensors offer high precision and can be miniaturized for use in various environments.
5. **Nanotechnology-based Biosensors:** Nanotechnology has enabled the development of highly sensitive and specific biosensors at the molecular scale. Nanoparticles, nanowires, and nanotubes

can be functionalized with specific biomolecules to detect target analytes with high precision. These biosensors are particularly advantageous for detecting low-abundance biomolecules and monitoring subcellular processes.

Each type of live-cell biosensor offers distinct advantages and can be selected based on the specific requirements of the research or application. The integration of these diverse biosensor types continues to enhance our ability to study and manipulate living cells, driving advancements in biomedical research, diagnostics, and therapeutic development [34, 35, 36, 37, 38, 39].

There are three main categories of live-cell biosensors:

1. **Cell-free Biosensors:** These biosensors do not involve living cells and instead rely on isolated biomolecules like enzymes, antibodies, or nucleic acids as the sensing element.
2. **Nonspecific Whole-cell Biosensors:** In these biosensors, the entire living cell acts as a nonspecific sensing element, responding to various environmental stimuli or conditions without targeting specific analytes.
3. **Specific Whole-cell Biosensors:** These biosensors utilize genetically engineered living cells as specific sensing elements, designed to detect and respond to particular analytes or conditions.

Biosensors can also be classified based on their detection mechanism, with two main categories [40, 40]:

- **Label-based Biosensors:** These biosensors rely on the use of labels or markers, such as fluorescent dyes, enzymes, or radioactive isotopes, to generate a measurable signal upon interaction with the target analyte.
- **Label-free Biosensors:** These biosensors do not require labels or markers, instead detecting changes in physical properties like mass, conductivity, or refractive index upon interaction with the target analyte.

Various fabrication techniques are employed in the development of biosensors, including:

- Photolithography
- Computer Numerical Control (CNC) machining
- Casting
- 3D printing

Electrochemical biosensors are a prominent category, encompassing techniques like [41, 42]:

- **Electric Cell–Substrate Impedance Sensing (ECIS):** Monitors cell adhesion, proliferation, growth, and viability in real-time by measuring the impedance between cells and a substrate.
- **Field-effect Transistor (FET) Sensors:** Detect extracellular microenvironments and electrophysiological activity of cells.
- **Potentiometric-based Sensors:** Detect target substances like hydrogen peroxide (H2O2) released from living cells.

Cell sensor technology has enabled the development of various live-cell biosensor platforms, such as:

- **Genetically-encoded Fluorescent Biosensors:** Utilize genetically engineered fluorescent proteins or RNA aptamers to detect specific analytes or cellular processes.
- **Impedance-based Biosensors:** Monitor cellular behavior and responses by measuring changes in electrical impedance.

- **Whole-cell Electrochemical Biosensors:** Employ living cells as the sensing element, coupled with electrochemical detection techniques.
- **Microfluidic-integrated Cell-based Assays:** Combine living cells with microfluidic devices for controlled and automated analysis [43, 44, 45].

3. Principles of Live-Cell Biosensors

Live-cell biosensors are designed to monitor and report on the physiological and biochemical states of living cells in real-time. The underlying principles of these biosensors revolve around the interaction between biological components and physical transducers that convert biological responses into measurable signals (Fig. 4).

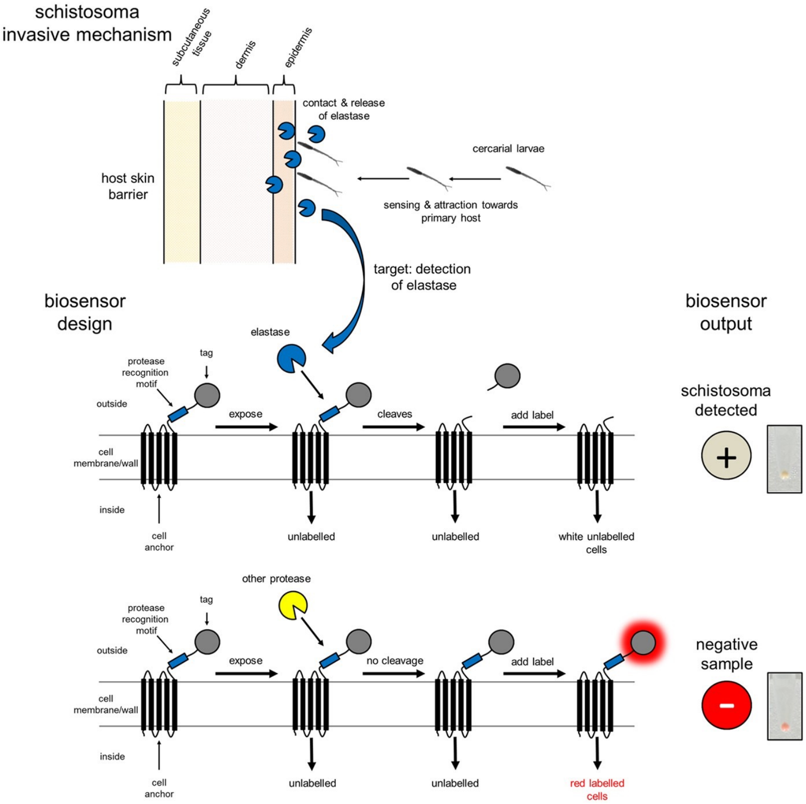

Figure 4. Detection of Schistosoma mansoni via cercarial elastase activity.

1. **Biological Recognition Elements:** At the core of live-cell biosensors are biological recognition elements such as enzymes, antibodies, nucleic acids, or whole cells. These elements are responsible for the specific detection of target analytes or cellular conditions. For instance, enzymes can catalyze reactions with specific substrates, while antibodies can bind to particular antigens, triggering a measurable response [46].
2. **Signal Transduction:**
   The interaction between the biological recognition elements and the target analytes generates a signal that must be transduced into a detectable form. This is achieved through various transduction mechanisms, including optical, electrochemical, and mechanical methods. For example, fluorescence-based biosensors use changes in fluorescence intensity or wavelength to indicate

the presence of specific molecules or changes in cellular conditions [47].

3. **Real-time Monitoring:** A key advantage of live-cell biosensors is their ability to provide continuous, real-time monitoring of cellular processes. This allows researchers to observe dynamic changes and transient events within cells, offering insights that static assays cannot provide. Techniques such as fluorescence resonance energy transfer (FRET) enable the detection of real-time molecular interactions and cellular activities [48].
4. **Data Analysis:** The signals generated by live-cell biosensors must be accurately measured and analyzed. Advanced data analysis techniques, often incorporating artificial intelligence and machine learning, are used to interpret the complex data, identify patterns, and make predictions about cellular behavior and responses [49].

By integrating these principles, live-cell biosensors provide powerful tools for advancing our understanding of cellular processes and enhancing applications in diagnostics, drug discovery, and personalized medicine (Fig. 5) [50, 51].

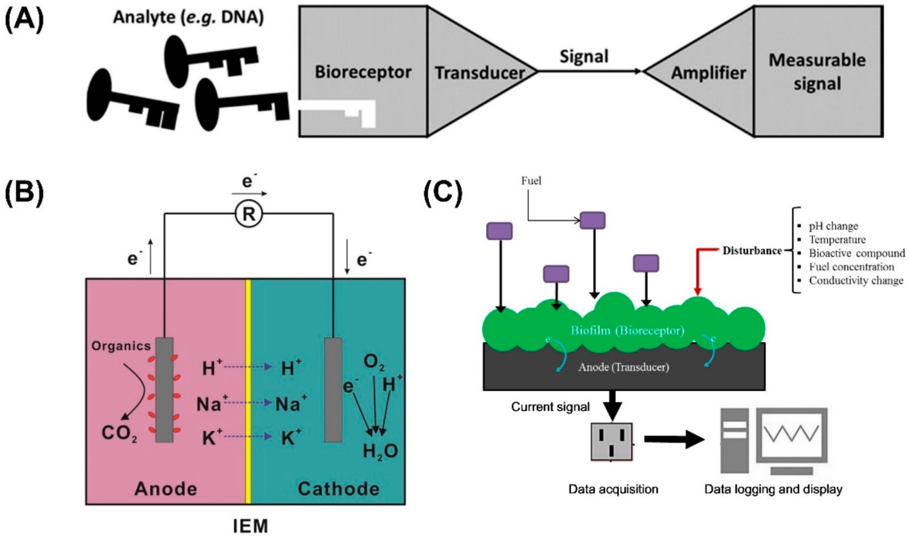

Figure 5. Schematic diagrams of (A) a biosensor, (B) a dual-chamber microbial fuel cell (MFC) and (C) an MFC-based biosensor.

The fundamental principle behind live-cell biosensors revolves around coupling a biological recognition element (probe) with a transducer device capable of converting biochemical interactions into measurable electrical signals [49]. This integration enables the detection and analysis of biological processes within living cells in a non-invasive and label-free manner [50].

The transduction mechanisms employed in biosensors encompass a diverse array of techniques, including:

- **Electrochemical:** Detecting changes in current, potential, or charge resulting from biochemical interactions.
- **Acoustic Wave:** Monitoring alterations in acoustic wave properties, such as frequency or phase, due to biochemical events.
- **Optical:** Measuring changes in optical properties, like absorbance, fluorescence, or refractive index, in response to biochemical interactions.

Key performance characteristics that define the efficacy of biosensors include [52, 53]:

- **Selectivity:** The ability to differentiate and specifically detect the target analyte or biological process from other interfering substances or events.
- **Sensitivity:** The capability to detect and quantify minute concentrations or changes in the target analyte or biological process.
- **Dynamic Range:** The range of analyte concentrations or biological responses that the biosensor can accurately measure.
- **Calibration:** The process of establishing a quantitative relationship between the measured signal and the concentration or level of the target analyte or biological process.
- **Label-free Operation:** The ability to detect and analyze biological interactions without the need for external labels or markers, enabling real-time monitoring of native cellular processes.

Live-cell biosensors offer several unique advantages, including:

- **Dynamic Cellular Monitoring:** The capacity to continuously track and observe dynamic cellular responses, providing insights into complex biological systems and their temporal evolution.
- **High Sensitivity and Specificity:** The potential for enhanced sensitivity and specificity due to the direct coupling of biological recognition elements with transducer devices, enabling precise detection and quantification of target analytes or processes.
- **Biological Relevance:** The ability to study biological processes within their native cellular environment, offering more physiologically relevant insights compared to cell-free or isolated systems.

Cell sensor technology has been instrumental in the development of various live-cell biosensor platforms, enabling researchers and scientists to probe and understand the intricate workings of living cells with unprecedented precision and detail [54].

4. Design and Engineering

The design and engineering of live-cell biosensors involve a multidisciplinary approach, combining principles from biology, chemistry, physics, and engineering to create devices capable of real-time cellular monitoring. The process begins with the selection of appropriate biological recognition elements, such as enzymes, antibodies, or genetically modified cells, which are tailored to detect specific target analytes or physiological changes (Fig. 6) [55, 56].

1. **Selection of Recognition Elements:** The choice of recognition elements is crucial for the specificity and sensitivity of the biosensor. These elements must have high affinity and selectivity for the target analyte to ensure accurate detection. For instance, enzymes can be chosen for their catalytic activity, while antibodies are selected based on their binding specificity to antigens.
2. **Transducer Integration:** The recognition elements are coupled with transducers that convert biological interactions into measurable signals. Common transducers include optical, electrochemical, and mechanical systems. Optical transducers might use fluorescence or absorbance changes, while electrochemical transducers detect changes in electrical properties such as current or voltage. Mechanical transducers measure physical changes like cell deformation or motility.
3. **Signal Amplification and Processing:** To enhance the sensitivity and reliability of the biosensor, signal amplification techniques are often employed. This can involve the use of nanomaterials, such as nanoparticles or quantum dots, which amplify the signal through their unique optical or electronic properties. Signal processing algorithms, sometimes incorporating artificial intelligence, are then used to interpret the amplified signals and provide meaningful data.
4. **Microfabrication and Miniaturization:** The engineering aspect includes microfabrication techniques to create miniaturized biosensors that can be integrated into microfluidic systems for high-

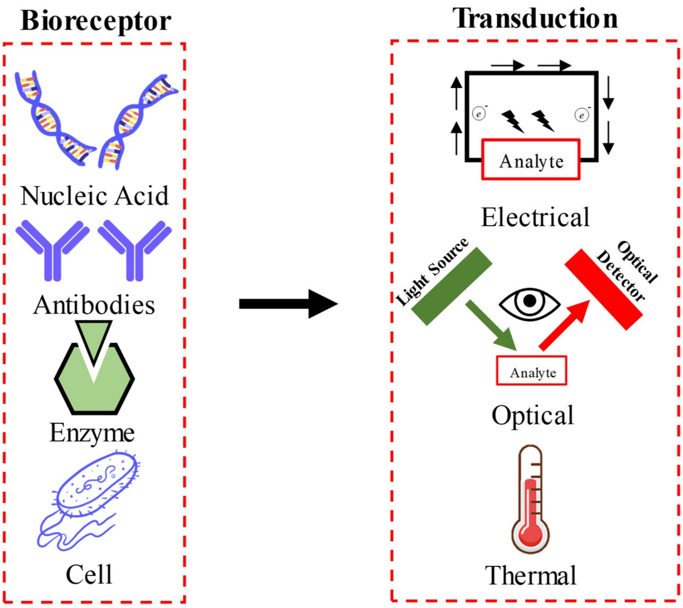

Figure 6. Biosensors based on different methods of transduction

throughput analysis. This miniaturization allows for the development of portable, low-cost devices suitable for various applications, from clinical diagnostics to environmental monitoring.

Through meticulous design and engineering, live-cell biosensors are optimized for performance, enabling precise, real-time monitoring of cellular activities and significantly advancing the field of biological sensing (Fig. 7) [57, 58, 59].

The design and engineering of live-cell biosensors involve a multidisciplinary approach, integrating principles from various fields such as synthetic biology, material science, and nanotechnology. Advances in synthetic biology have enabled the engineering of mammalian cells with new sensing and therapeutic functionalities, paving the way for the development of theranostic cell-based devices.

One of the critical aspects of biosensor design is the attachment of the probe, which serves as the biological recognition element. Several methods are employed for probe attachment, including:

- **Direct and Linker Adsorption:** The probe is immobilized on the transducer surface through physical adsorption or the use of linker molecules.
- **Entrapment and Encapsulation:** The probe is entrapped or encapsulated within a polymer matrix or membrane, allowing for selective permeation of analytes.
- **Covalent Binding:** The probe is covalently bound to the transducer surface, ensuring a stable and robust attachment.
- **Self-Assembled Monolayers (SAMs):** The probe is attached to the transducer surface through the formation of organized molecular assemblies.
- **Molecularly Imprinted Polymers (MIPs):** The probe is incorporated into a polymer matrix, creating specific binding sites for the target analyte.

Technical strategies employed in biosensor design can be broadly classified into two categories: label-based and label-free detection. Each approach has its advantages and limitations [60]:

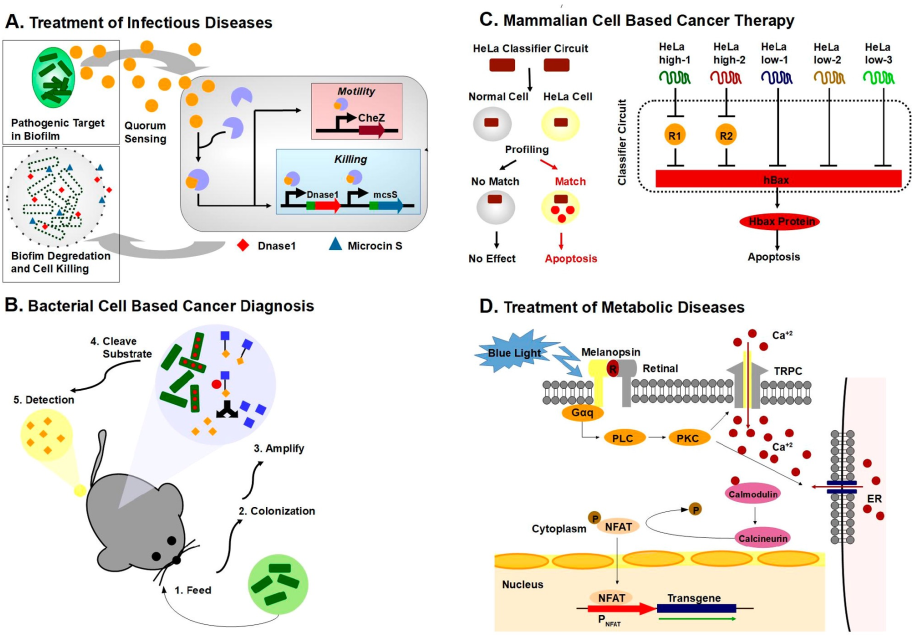

Figure 7. Cellular biosensors with complex genetic logic operations.

Table 1

Detection Method Advantages Limitations Label-based High sensitivity, well-established techniques Potential interference from labels, limited to specific analytes Label-free Real-time monitoring, no labeling required, versatile Lower sensitivity, complex data analysis

Current research trends in biosensor design focus on integrated approaches that combine multiple technologies, such as electrochemical, optical, and mechanical techniques, with biomaterials, polymers, and nanomaterials. This integration aims to achieve highly sensitive, miniaturized, and versatile biosensors. Furthermore, the development of label-free biosensors using techniques like surface plasmon resonance (SPR) and electric cell-substrate impedance sensing (ECIS) is gaining traction. These techniques enable real-time monitoring of cellular behavior and responses without the need for external labels, providing a more physiologically relevant understanding of biological processes [61, 62].

5. Signal Transduction and Detection

Electrochemical biosensors have emerged as powerful tools for detecting and analyzing biological processes within living cells in a non-invasive and label-free manner [63]. Various types of electrochemical biosensors have been developed, including:

- **Electric Cell-Substrate Impedance Sensing (ECIS) Platforms:** These systems monitor cell adhesion, proliferation, growth, and viability in real-time by measuring the impedance between cells and a substrate. ECIS-based 3D cell culture systems can more accurately evaluate the efficacy and toxicity of anticancer drugs compared to traditional 2D cultures.
- **Field-Effect Transistor (FET) Sensors:** FET-based sensors can detect extracellular microenvironments and electrophysiological activity of cells. For example, they can monitor extracellular acidification and pH changes in cancer cells in response to drug treatment.

- **Potentiometric-based Sensors:** These sensors can detect target substances like hydrogen peroxide (H2O2) released from living cells, serving as indicators of cellular metabolism and viability.

In addition to electrochemical techniques, optical/visual biosensors utilizing fluorescence, hydrogels, silica, quartz, and glass have demonstrated improved sensitivity and specificity. The incorporation of nanomaterials like gold, silver, and carbon-based materials has further enabled the development of highly sensitive and selective biosensors. Genetically encoded or synthetic fluorescent biosensors have provided unprecedented insights into biological processes at the single-molecule level. These biosensors leverage advances in synthetic biology, genetic engineering, and protein engineering to create novel sensing platforms. For instance, microbial biosensors developed through these techniques have found applications in environmental monitoring and bioremediation [64, 65].

Table 2.

Transduction/Detection Method Applications Electrical Cell-Substrate Impedance Sensing (ECIS) Monitoring cell adhesion, proliferation, and viability Light Addressable Potentiometric Sensors Detecting extracellular pH changes and cellular metabolism Fluorescent Imaging Visualizing biological processes at the single-molecule level

Combining different analytical techniques, such as impedance assays with amperometric or optical methods, provides enhanced understanding of dynamic cellular processes and enables multiparametric characterization of cell behavior. Moreover, innovative sensing concepts like optogenetic modulation of cellular reactivity have been developed, allowing rapid and sensitive detection of bioactive compounds by monitoring specific modifications in cellular dynamics induced by the analytes (see Fig. 8) [66, 67].

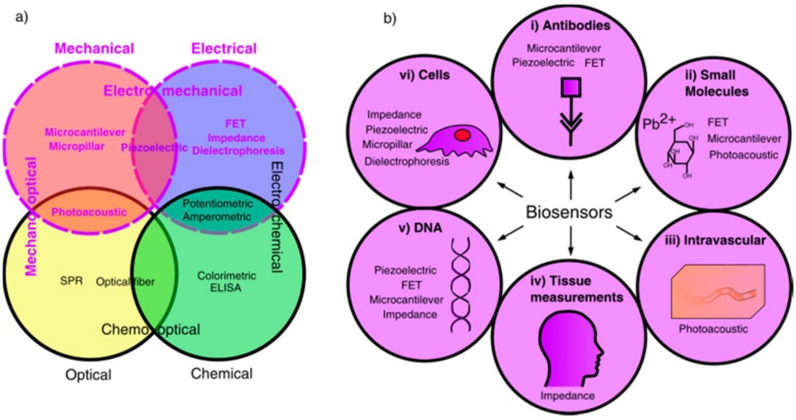

Figure 8. Biosensor applications and fields.

- radiation detector - electromagnetic fields - electromagnetic radiation - magnetic field - cell tower - EMF detection - extremely low frequency

5.1 Applications in Environmental Monitoring

Whole cell-based biosensors have shown immense potential for applications in environmental pollution detection and biomedical diagnostics. The most promising areas are medical diagnostics and environmental monitoring, with a focus on better integrating cellular sensors with nano and micro-scaled integrated chips to create real-time, portable devices for bedside diagnostics and remote environmental toxin detection. Biosensors are analytical devices that leverage biological sensing elements to detect and quantify environmental pollutants like heavy metals and organic compounds.

Unlike traditional chemical analysis methods, biosensors can provide valuable information on the bioavailability and toxicity of pollutants, offering a more comprehensive understanding of their impact on living organisms [68, 69].

Compared to conventional methods, biosensors offer several advantages, including:

- Low cost
- Energy efficiency
- Portability
- Real-time monitoring capabilities

These advantages make biosensors highly attractive for environmental monitoring applications, contributing to achieving several Sustainable Development Goals (SDGs) related to clean water, responsible consumption, climate action, and protecting terrestrial and marine life.

5.2 Heavy Metal Detection

Biosensors have been developed to detect various heavy metals, such as arsenic (As), lead (Pb), cadmium (Cd), mercury (Hg), chromium (Cr), copper (Cu), and zinc (Zn), in environmental samples. These biosensors enable real-time, in-situ monitoring of bioavailable heavy metals in water, wastewater, soil, and sediment samples, providing crucial information for environmental risk assessment and remediation efforts.

5.3 Organic Pollutant Monitoring

In addition to heavy metals, biosensors can detect a wide range of organic pollutants, including:

- Pesticides
- Herbicides
- Hydrocarbons
- Surfactants
- Persistent organic pollutants (POPs)

The ability to continuously monitor organic pollutants in environmental samples in real-time is a significant advantage of biosensor technology, enabling timely detection and mitigation of potential environmental hazards. Cell sensor technology has played a pivotal role in the development of these biosensors, enabling the integration of living cells with microelectronic devices for sensitive and specific detection of environmental contaminants [70, 71].

6. Biomedical Applications

Bioelectrical impedance cell culture platforms have demonstrated broad utility in biomedical applications and cancer research, enabling the assessment of subtle cellular responses to various stimuli. These platforms leverage advances in synthetic biology to engineer mammalian cells with customized sensing and therapeutic functionalities, paving the way for the development of theranostic cell-based devices (Fig. 9) [72, 73].

Biosensors have a wide range of applications in tissue engineering, including:

- Monitoring cell polarity, metabolism, proliferation, and differentiation

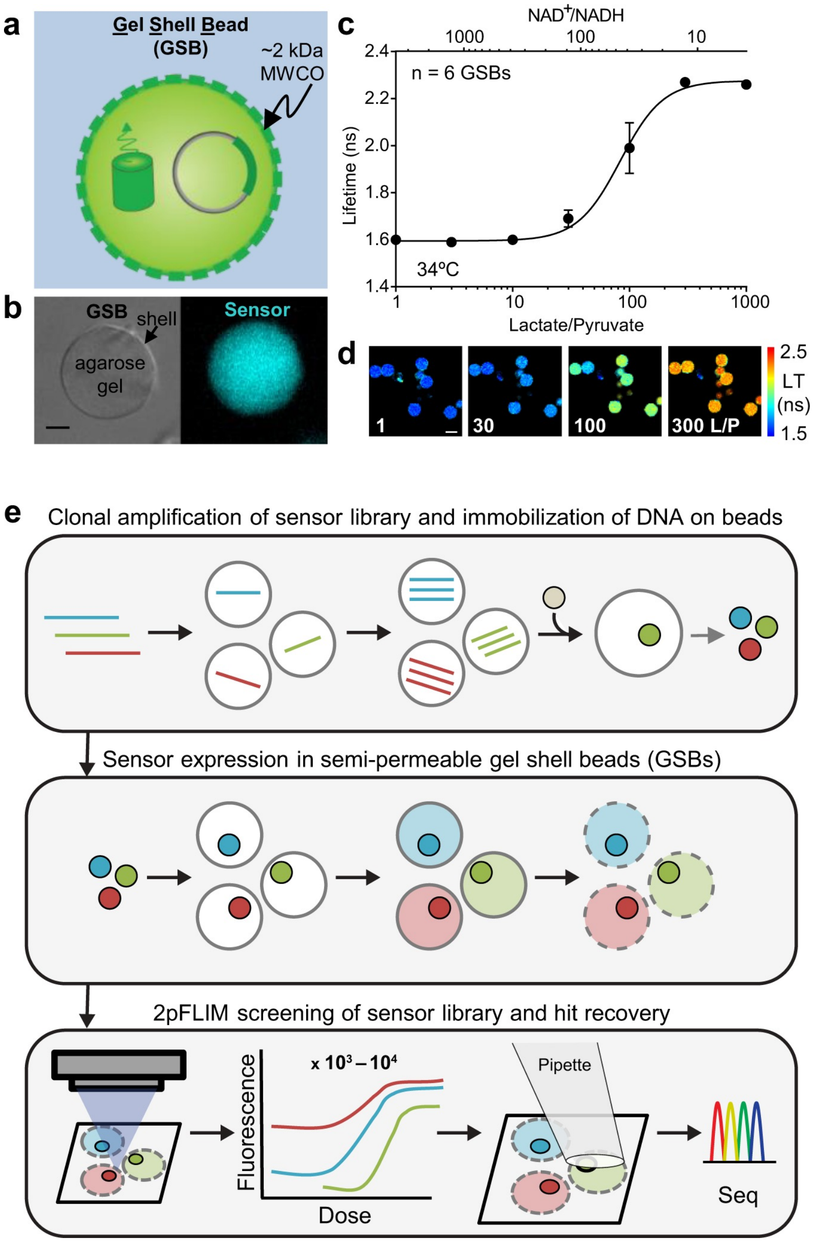

Figure 9. GSBs as a platform for screening genetically encoded fluorescent biosensors.

- Detecting cellular signals and responses, such as electrophysiological properties, secretion of signaling molecules, and cell-material interactions
- Creating organ-on-a-chip and other biomimetic tissue models to study disease mechanisms and test drugs
- Specific applications in neural, cardiac, and other tissue disease models

Electrochemical biosensors have been particularly useful in [74]:

1. **Anticancer Drug Testing:** 3D cell culture models and Electric Cell-Substrate Impedance Sensing (ECIS)/Microelectrode Guided Impedance Spectroscopy (MGIS) platforms can more accurately evaluate the efficacy of anticancer drugs compared to traditional 2D cell models. Key findings suggest that 3D ECIS/MGIS platforms can better differentiate the effects of varying anticancer drug concentrations on 3D lung cancer models compared to 2D models.
2. **Stem Cell Monitoring:** These biosensors can detect pluripotency, differentiation, and functions of stem cells in a non-destructive manner , enabling real-time monitoring of stem cell behavior and responses.

Cell sensor technology has revolutionized biomedical research by providing powerful tools for studying cellular processes, evaluating drug efficacy, and developing advanced tissue engineering applications, ultimately contributing to the development of more effective diagnostics and therapeutic strategies [75, 76, 77].

7. Challenges and Limitations

Live-cell biosensors, while transformative, face several inherent challenges and limitations. One significant challenge is ensuring the stability and longevity of the sensors. Living cells are dynamic and sensitive to environmental conditions, which can affect the biosensor's performance over time. Maintaining cell viability and functionality under varying conditions is essential for reliable long-term applications. Additionally, ensuring biocompatibility presents a significant hurdle; the materials and components used must not adversely impact the cells or interfere with their natural functions. Achieving a balance between sensitivity and biocompatibility is critical for accurate data collection [78, 79, 80].

Another challenge is the signal-to-noise ratio. Background noise and nonspecific interactions can obscure the true signal, reducing the biosensor's accuracy. Advanced signal processing and noise reduction techniques are required to enhance signal clarity. The complexity of cellular systems adds another layer of difficulty. Cellular responses are influenced by numerous factors, making it challenging to isolate specific signals. Biosensors must be precisely designed to target and measure intended analytes without interference from other cellular processes (Fig. 10) [81, 82].

Finally, integrating biosensors with robust data analysis tools is crucial. The vast amounts of data generated need sophisticated algorithms and machine learning techniques to identify patterns and derive actionable insights. Addressing these challenges through continuous research and technological advancements is key to unlocking the full potential of live-cell biosensors in various fields, from medical diagnostics to environmental monitoring. Despite the remarkable potential of cell sensor technology and live-cell biosensors, several challenges and limitations need to be addressed (Fig. 11) [83, 84, 85]:

- **Standardization:** The lack of standardized protocols and methodologies for biosensor development and validation hinders widespread adoption and reproducibility across different research groups and applications [86].

- **Storage and Stability:** Many biosensors suffer from reduced storage life and stability during transportation, limiting their practical applications in field settings or remote locations.

- **Interference and Specificity:** Complex environmental samples or biological matrices can introduce interferences, reducing the specificity and accuracy of biosensors. Achieving high selectivity for target analytes in real-world scenarios remains a significant challenge [87].

- **Sensitivity Limitations:** While nanomaterials like gold, silver, silicon, and carbon-based materials have been explored to enhance sensitivity, issues related to toxicity and large-scale production pose obstacles to their widespread implementation.

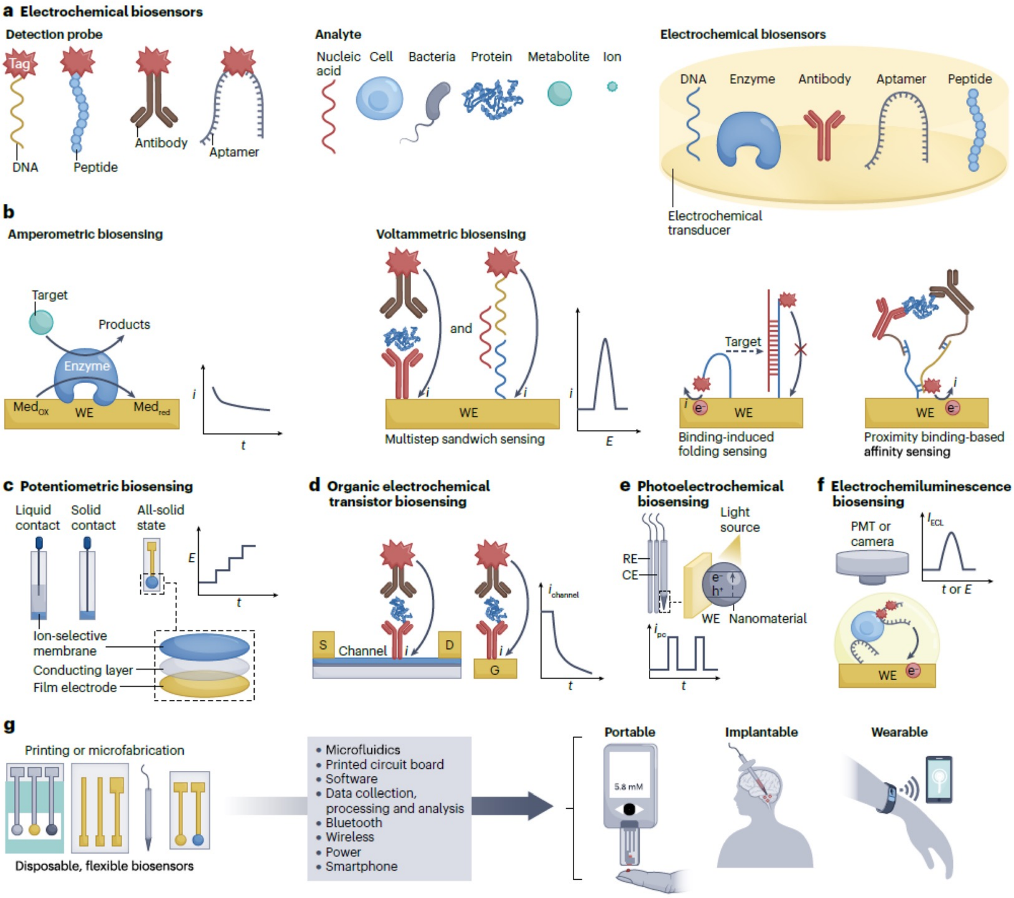

Figure 10. Presentation of the electrochemical biosensors.

- **Data Acquisition:** Biosensors often provide a one-shot or snapshot information rather than continuous time-course data, limiting their ability to capture dynamic biological processes and temporal changes [88].

To address these challenges, ongoing research efforts focus on:

- Developing standardized protocols and validation methods for biosensor development and testing.
- Exploring new materials and immobilization strategies to improve storage stability and shelf life.
- Implementing advanced signal processing and data analysis techniques to enhance selectivity and minimize interference from complex samples.
- Investigating biocompatible and scalable nanomaterials to improve sensitivity without compromising safety or cost-effectiveness.
- Integrating biosensors with microfluidic systems and continuous monitoring platforms to enable real-time, time-course data acquisition.
  Overcoming these challenges through interdisciplinary research and innovation will be crucial for realizing the full potential of cell sensor technology and live-cell biosensors in various applications, from environmental monitoring to biomedical diagnostics and therapeutics [89, 90].

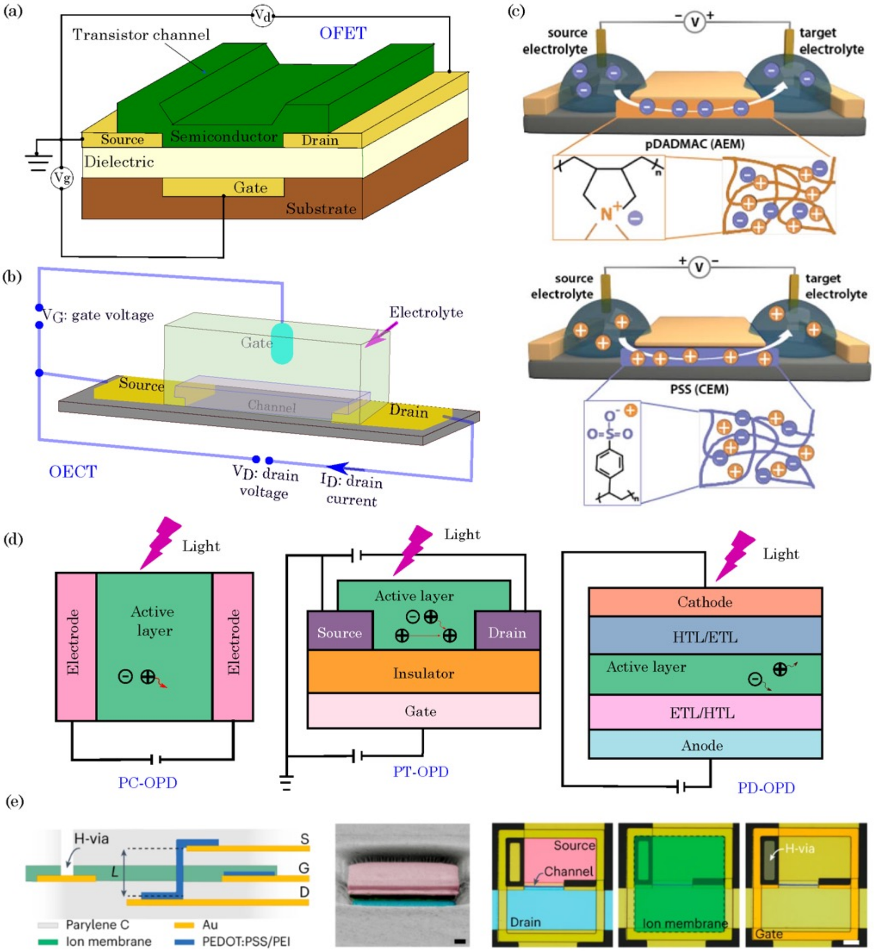

Figure 11. organic field-effect transistors (OFETs)

8. Recent Advancements and Future Directions

The field of live-cell biosensors has witnessed remarkable advancements, driven by the growing demand for real-time, in situ monitoring and analysis in various domains, including drug discovery, biomedicine, food safety, defense, security, and environmental monitoring. Rapid developments in microelectronics and information technologies have played a pivotal role in enhancing the performance and capabilities of these sensors [91, 92, 93].

One of the key areas of focus is the development of portable, real-time, and in situ whole cell-based biosensors for environmental monitoring and medical diagnostics. These advancements aim to enable on-site analysis and decision-making, eliminating the need for time-consuming laboratory-based testing and analysis [94]. Ongoing research efforts in the field of live-cell biosensors are multifaceted, encompassing several critical objectives:

1. **Improving Stability and Robustness:** Enhancing the long-term functionality and operational stability of biosensors is crucial for their practical implementation in real-world scenarios. Researchers are exploring new materials, immobilization strategies, and engineering approaches to

ensure biosensors can withstand various environmental conditions and maintain their performance over extended periods [95, 96, 97, 98].

2. **Enhancing Sensitivity and Selectivity:** Achieving high sensitivity and selectivity remains a significant challenge, particularly in complex environmental or biological matrices. Researchers are investigating novel nanomaterials, signal amplification techniques, and advanced signal processing algorithms to improve the ability of biosensors to detect and quantify target analytes with high accuracy and minimal interference [99, 100].
3. **Multiplexing Capabilities:** The development of multiplexed biosensors capable of simultaneously detecting and analyzing multiple analytes or biological processes is a key area of focus. This capability would enable comprehensive analysis and provide a more holistic understanding of complex systems, such as environmental ecosystems or disease mechanisms [101, 102].
4. **Integrated Platforms:** Researchers are working towards developing integrated platforms that seamlessly combine sample preparation, biosensing, data analysis, and decision-making capabilities. These integrated systems aim to streamline the entire process, from sample collection to data interpretation, enabling rapid and efficient analysis in various settings, including point-of-care diagnostics and environmental monitoring [103, 104].

The future of live-cell biosensors lies in the successful integration of these advancements, enabling the development of highly sensitive, selective, and robust sensing platforms that can provide real-time, in situ analysis and decision-making capabilities across various fields [105, 106].

9. Conclusion

The revolutionary impact of cell sensor technology on live-cell biosensors has been profound, enabling unprecedented insights into the intricate workings of living cells. These biosensors have found wide-ranging applications in fields such as environmental monitoring, biomedicine, and drug discovery, offering sensitive, specific, and real-time analysis of biological processes. While significant advancements have been made, challenges such as standardization, storage stability, and interference still need to be addressed. Ongoing efforts in developing portable, integrated platforms, enhancing sensitivity and selectivity, and exploring novel materials and signal processing techniques hold the key to unlocking the full potential of this transformative technology. The future of live-cell biosensors is promising, poised to revolutionize our understanding of complex biological systems and drive innovations in various sectors.

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