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Review

Functional Organic Electrochemical Transistor-Based Biosensors for Biomedical Applications

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Abstract: Organic electrochemical transistors (OECTs), as an emerging device for the development of novel biosensors, have attracted more and more attention in recent years, demonstrating their promising prospects and commercial potential. Functional OECTs have been widely applied in the field of biosensors due to their decisive advantages, such as high transconductance, easy functionalization, and high integration capability. Therefore, this review aims to provide a comprehensive summary of the most recent advances in the application of functional OECT-based biosensors in biomedicine, especially focusing on those biosensors for the detection of physiological and biochemical parameters that are critical for the health of human beings. First, the main components and basic working principles of OECTs will be briefly introduced. In the following, the strategies and key technologies for the preparation of functional OECT-based biosensors will be outlined and discussed with regard to the applications of the detection of various targets, including metabolites, ions, neurotransmitters, electrophysiological parameters, and immunological molecules. Finally, the current main issues and future development trends of functional OECT-based biosensors will be proposed and discussed. The breakthrough in functional OECT-based biosensors is believed to enable such devices to achieve higher performance, and thus, this technology could provide new insight into the future field of medical and life sciences.

Keywords: organic electrochemical transistor; biosensor; functional device; biomedicine; bioanalysis

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1. Introduction

Since Luigi Galvani discovered bioelectricity in the 18th century, researchers in bioelectronics have been continuously contributing to this field. In 1947, the transistor was invented under the efforts of William Shockley, which brought about a revolution in microelectronics. A transistor is an electronic device with a wide range of applications, usually consisting of a gate, source, drain, an insulating layer under the gate, and semiconductor materials. By applying a voltage to the metal electrode to regulate the number of movable electrons (n-type) or holes (p-type) inside the semiconductor, the conductivity of the device can be controlled, or changes in electrical parameters can be induced. In the 1980s, Wrighton creatively introduced transistors into biology, undoubtedly pioneering a new tool: the organic electrochemical transistor (OECT) [1].

Since Updike et al. developed the first biosensor in 1967, biosensing technology has gradually become an indispensable and important detection tool in biomedical fields [2]. Since then, it has been widely studied for its ability to track biological activities. At present, OECTs have been used as neural recording elements, ion sensors, biomolecule detectors, and cell activity monitors. Functional OECT-based biosensors typically combine the signal transduction and amplification functions of specific biological systems. The stability and biocompatibility of OECTs are key requirements for their application in bioelectric devices, whose properties are typically evaluated through in vivo and in vitro experiments [3,4].

Therefore, in order to obtain a stable biosensing function, OECTs need to undergo biological functionalization treatment. More recently, organic mixed ion electronic conductors (OMIECs) have attracted more and more attention due to their solution processability, flexibility, and biocompatibility [5,6]. These materials are capable of operating in aqueous environments under low voltage, thereby forming a good sensing interface with living organisms. Based on these characteristics, OECT technology has demonstrated great potential in developing high-sensitivity, flexible, and stable biosensors.

Here, we mainly explore the new discoveries in the field of functional OECT-based biosensors over the past few years, especially those for biomedical applications. Firstly, we briefly introduce the composition, working principle, and common channel layer materials in OECT devices. Then, specific biosensing applications will be discussed, including metabolite sensors, ion sensors, neurotransmitter sensors, cellular electrophysiological recordings, and other types of organisms. We mainly focus on the materials and construction innovations used in these applications and compare the performances of these devices (Figure 1). Finally, the challenges and opportunities faced by the selection of OECT channel layer materials are discussed in detail.

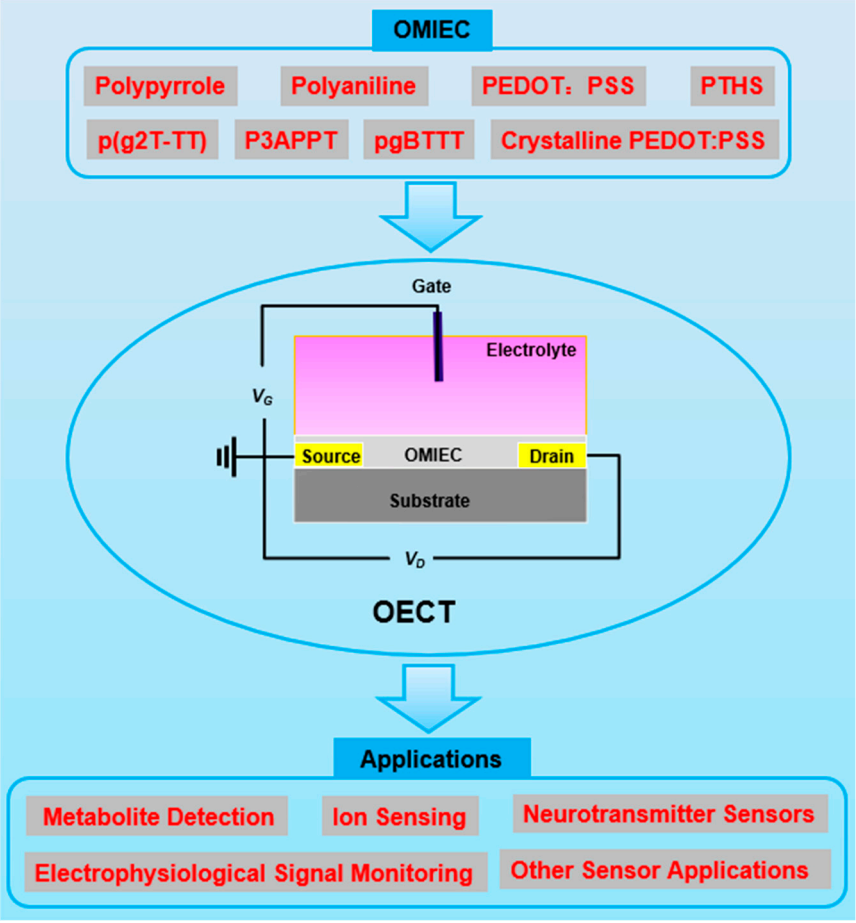

Figure 1. Schematic diagram showing the development of various functional OECTs with various OMIECs towards different applications.

2. Basic Principles and Performances of OECT

Traditional metal oxide semiconductor field-effect transistors (MOSFETs) operate based on field effects, controlling the formation and disappearance of conductive channels by applying voltage to the gate, thereby regulating current flow. The work of OECTs is based on electrochemical doping, and currently, most OECTs adopt a three-terminal system structure with a source, drain, and gate. Fill the channel material between the source and drain, i.e., OMIECs, through which both electronic and ionic charges are

transferred. The source and drain electrodes are usually made of metallic gold because the work function of gold is approximately 5 eV, which matches the energy levels of the hole and electron injection well and provides good environmental stability [7]. The gate electrode is then immersed in an electrolyte rich in mobile ions, which come into direct contact with the channel material. Electrolytes could be solid or liquid, depending on the specific application [5]. Meanwhile, in order to achieve better biocompatibility, liquid-based electrolytes are usually used when using biological system interfaces. During the operation of OECTs, a bias voltage (V_D) is applied between the source and drain to drive the current (I_D) through the channel. The magnitude of this current is controlled by the input voltage (V_G) at the gate, which affects the electrolyte to extract ions or inject ions into the channel, thereby controlling the doping level of the material. Channel materials can be classified based on their ability to transport holes (p-type) or electrons (n-type) as electron charge carriers. Unlike traditional transistors, OECTs use OMIECs as the material, which are typically a conjugated polymer, giving OECTs a high degree of flexibility and biocompatibility. By changing the organic electrolyte, the conduction voltage of the device can be altered, which is also the main working principle of the biosensor developed based on OECTs. In addition, the high biocompatibility also makes OECTs suitable for many applications in current bioelectronics and biomedical fields [5].

So far, among all the materials used as OECT channel materials, the most widely used and extensively studied OMIEC is the conjugated polymer composite material, i.e., poly (styrene sulfonate)-doped poly (3,4-ethylenedioxythiophene) (PEDOT:PSS), which was developed by Bayer in the late 1980s [8]. PEDOT:PSS has a wide range of commercial availability, good biocompatibility, and relatively high steady-state performance, so there have been many studies and applications related to this OMIEC [9–14]. Its p-type properties stem from its electron-rich polythiophene backbone, which gives the material a shallow HOMO (highest occupied molecular orbital). In this system, the conjugated PEDOT main chain provides a pathway for hole transport, while the hydrophilicity of PSS polyanions is responsible for absorbing water into the material, thereby creating an effective ion conduction pathway in and out of the material. Therefore, under the most basic conditions, ion conduction in OMIEC is achieved by introducing hydrophilicity. PEDOT:PSS has been proven to be excellent as an OMIEC in both theoretical and experimental research [15]. However, at the same time, this material also has an important problem, which is poor conductivity due to structural issues. This has led to the long-standing criticism of PEDOT:PSS has an edge channel layer material for OECTs, which directly affects the performance of OECTs [16,17]. There are currently many studies on improving PEDOT:PSS, which can be roughly divided into two types: one is heat and light treatment [18,19], while the other one is the addition process (adding organic solvents, salts, ions, etc.) [16,20–22].

In order to solve the problem of PEDOT:PSS and improve the device performance, in 2014, sulfonate polythiene derivatives (PTHS) were used in the OECT channel to promote ion penetration and ion movement in the film body without the need for a separate ion conductive phase like PEDOT:PSS [23]. In 2018, the trapezoid conjugated polymer poly (benzimidazobenzophenanthroline) (BBL) was introduced into OECTs. Surprisingly, BBL still exhibits excellent performance as an OMIEC even though it does not contain hydrophilic side chains [24,25]. Table 1 enumerates the OECT parameters using different OMIECs.

Table 1. OECT device parameters with different OMIECs were used.

OMIEC	Gm (mS)	μC* (F cm^{-1}V^{-1}s^{-1})	Ref.
Polypyrrole	0.1	-	[1]
Polyaniline	0.4	-	[26]
PEDOT:PSS	1.2	-	[27]
PTHS	3.5	-	[23]
pgBTTT	-	563	[28]
p(g2T-TT)	-	90	[28]
P3APPT	-	31	[29]
Crystalline PEDOT:PSS	-	1568	[30]

A significant feature of the OECT is ability to operate in low voltage conditions, typically described by transfer curves to illustrate the relationship between drain current and gate voltage (Figure 2a) [31–33]. The common testing method is to give one gate voltage or drain voltage, then change the other one, observing the change in drain current. The description of this conversion efficiency is called transconductance, characterized by g_m, which is usually a parameter of some types of transistors and amplifiers. It can be calculated by $g_m = \partial I_D / \partial V_g$, which represents the amplification effect of electronic components. In addition, the OECT has a high transconductance value, which is originated from its unique structure and working principle (Figure 2b,c) [34].

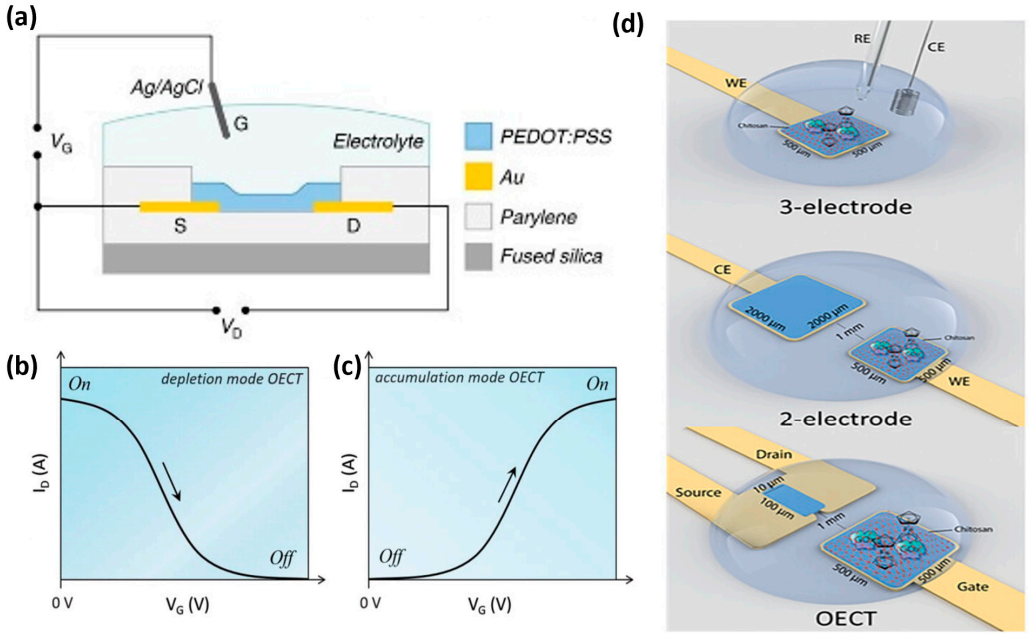

Figure 2. Schematics of structure and principle of OECT for in vitro bioelectronics. (**a**) A common cross-sectional schematic diagram of OECT [34]. (**b**) Transfer curve of depletion mode OECT. At V_G = 0 V, the transistor conducts and high current flows in the channel, as the channel is prepared using doped conductive polymers. When V_G is applied, electrolyte cations replace polymer holes, ultimately shutting down the transistor. (**c**) The transfer curve of cumulative mode OECT. At V_G = 0 V, the transistor is turned off and a small current flows in the channel because it is prepared using a polymer with poor conductivity. When V_G is applied, electrolyte anions are injected into the channel, which causes the transistor to conduct [33]. (**d**) Functionalized PEDOT:PSS electrodes serve as WE for 3-e and 2-e systems (top and middle, respectively) and as gate electrodes for OECT (bottom) [35].

From recent years of research, we can learn another more detailed calculation method by the following equation:

$$g_m = \frac{Wd}{L}\mu C^*(V_{Th} - V_G)$$

where W is the channel width, d is the channel thickness, L is the channel length, μ is the electron charge carrier mobility, C^* is the volumetric capacitance (a measure of the material's ability to conduct ion charges), and V_{Th} is the threshold voltage.

From this equation, it can be seen that g_m is influenced by the geometric shape of the device (W, d, and L) as well as the material properties (mobility and volumetric capacitance). Therefore, a simple way to improve g_m is to adjust the device size. Although theoretically it is possible to maximize g_m by changing the area size, the biological application of the OECT requires reducing the device area. So, the commonly used research method is to increase the thickness of the channel to improve g_m. However, as the thickness of the device increases, its response time also slows down, which limits the operating frequency of the device. Therefore, an effective strategy is to optimize the electronic and ionic properties of channel

materials to maximize the product of μC^*. It is recommended to use μC^* as a quality factor independent of geometric shape, as it can more accurately reflect the performance of the OMIEC [36].

In the existing technology, most electrochemical sensors have a 3-electrode (3-e) structure (Figure 2d), which has significant differences in parameters compared to other types of sensors (Table 2). They are the working electrode (WE), counter electrode (CE), and reference electrode (RE). The WE is the part that directly reacts with the measured targets, usually made of catalytic materials, which can react with the measured substance. The CE and WE work together to circulate current through circuits, ensuring the continuous progress of electrochemical reactions. The counter electrode usually does not participate in specific chemical reactions, but its surface area and material properties can affect the overall performance of the sensor. The RE provides a stable potential reference point, which is crucial for maintaining the accuracy and stability of electrochemical sensors [35]. Unlike this structure, the OECT electrochemical sensors usually do not have RE settings. The OECT relies on changes in the electrochemical potential of the gate, source, and drain to alter the conductivity of the channel and observe changes in the drain current (I_d). Many studies have demonstrated the advantages of the OECT in terms of signal-to-noise ratio (SNR), detection limit (LOD), and settling time [35,37].

Table 2. Comparison of sensor parameters obtained with different configurations [35].

Configuration	LOD (μM)	SNR (dB)	Working Range	Stabilization Time at 1 mM Glucose (s)
3-electrode	334 ± 88	59.5	334 μM–10 mM	1019 ± 310
2-electrode	429 ± 34	53.9	429 μM–1 mM	379 ± 81
OECT	130 ± 43	71.5	130 μM–1 mM	125 ± 66

3. Applications of Functional OECT-Based Biosensors

Nowadays, bioelectronic devices have been widely utilized in a large number of healthcare-related applications, such as implants [38], sensors [39], and nanomachines [40]. The OECT, due to its unique structure and performance, has attracted much attention for its ability to flexibly change its detection substance with the replacement of the OMIEC [41]. Specifically, as summarized in Table 3, the OECT has been used for various applications, such as metabolite detection [42], ion monitoring [43,44], neurotransmitter detection [45,46], cell activity monitoring [47], and environmental monitoring [48]. The detection capability of OECT sensors based on redox reactions does not depend on specific instruments, and their miniaturized design does not result in a decrease in sensitivity. In addition, the transistor configuration and built-in amplification capability of the OECT help amplify weak signals of low-concentration analytes, thereby effectively improving sensitivity.

Table 3. Performance of OECT-based biosensors towards biomedicine.

Targets	LOD	Linear Range	Sensitivity	Sensitive Elements	References
Glucose	1 nM	-	-	GOx	[42]
Glucose	0.02 mM	0.1–0.5 mM	0.12 $mA \cdot M^{-1} \cdot cm^{-2}$	GOx	[49]
L-Trp	0.01 μM	-	19.67 $\mu A \cdot \mu M^{-1}$	L-AAODX	[50]
L-Tyr	0.01 μM	-	16.71 $\mu A \cdot \mu M^{-1}$	L-AAODX	[50]
L-Phe	0.01 μM	-	15.51 $\mu A \cdot \mu M^{-1}$	L-AAODX	[50]
Lactate	-	10 μM -10 mM	-	LOx	[51]
Lactate	0.04 mM	0.1–2.5 mM	-	LOx	[49]
Urea	100 μM	0.1–20 mM	-	Urease	[52]
NT-proBNP	0.0026 $pg \cdot mL^{-1}$	0.003–3000 $pg \cdot mL^{-1}$	-	anti-NT-proBNP antibody	[53]
SARS-CoV-2 IgG	-	10 fM–100 nM	-	SARS-CoV-2 spike protein	[54]
Na^+	0.75 mM	-	-	[MTEOA] [$MeOSO_3$]	[55]
K^+	0.8 mM	-	-	[MTEOA] [$MeOSO_3$]	[55]
H^+ (pH)	-	-	3363.6 μA/pH	PANI	[56]

Table 3. *Cont.*

Targets	LOD	Linear Range	Sensitivity	Sensitive Elements	References
DA	1 nM	1 nM–30 μM	1.065 $\mu A \cdot \mu M^{-1}$ cm^{-2}	Nafion/rGO/CSF	[57]
DA	34 nM	0.4–10 μM	-	o-MIP/Pt	[46]
DA	170 nM	1–300 μM	0.326 $\mu A \cdot \mu M^{-1}$ cm^{-2}	NOCC-O	[45]
AA	260 nM	5–1000 μM	0.141 $\mu A \cdot \mu M^{-1}$ cm^{-2}	NOCC-R	[45]
IL-6	24 pM	-	-	Aptamer	[58]
Nitrite	0.1 nM	-	-	(Au-NPs)/rGO	[59]
DNA	5.75×10^{-14} M	0.1 pM–1 nM	-	SH-DNA	[60]
Escherichia coli	103 cfu mL^{-1}	-	-	Anti-*E. coli* O157:H7 antibody	[61]

(GOx: glucose oxidase; L-Trp: L-tryptophan; L-Tyr: L-Tyrosine; L-Phe: L-phenylalanine; L-AAODX: L-amino acid oxidases; LOx: lactate oxidase; DA: Dopamine; AA: Ascorbic Acid; IL-6: Interleukin-6; NT-proBNP: N-terminal pro-B-type natriuretic peptide).

3.1. Application of OECT-Based Biosensors in Metabolite Detection

Metabolites, which are intermediate or final products of metabolism, are a common indicator used in medical detection, including carbohydrates (such as glucose), amino acids, and lipid metabolites. Glucose is the most important metabolite used for medical detection. As the main source of energy for the human body, glucose participates in various cellular functions, such as the transmission of electrical signals in neurons, active transport, and synthesis of biochemical compounds. Any abnormality of glucose level or its regulation will lead to serious health conditions, such as diabetes and other related diseases. With the increasing number of diabetic patients, many diabetic patients or potential patients have a great demand for portable glucose sensors in order to know their condition in real time.

The history of glucose sensors can be traced back to the design of Clark and Lyons in 1962 [62]. Subsequently, in 1967, their design was implemented by Updike, and the first biosensor was manufactured [2]. This groundbreaking invention not only pioneered the field of biosensor technology but also laid the foundation for glucose sensors, an important branch of biosensors. There are data indicating that glucose sensors account for over 80% of the market share [63]. In recent years, glucose sensors have gradually developed towards portability and miniaturization [64]. At present, glucose oxidase (GOx) has become one of the most commonly used enzymes due to its high selectivity for glucose and stability under pH and temperature conditions compared to other enzymes. This is also the basis of many glucose biosensors, which have both high selectivity and sensitivity [65,66].

More recently, new methods have emerged that break away from the traditional method's dependence on enzymes [67]. In 2021, Koklu et al. combined an n-type OECT with a microfluidic chip to achieve real-time monitoring of glucose. The integration of microfluidics increases the conduction current and transconductance of n-type devices. Microfluidic integrated photoelectric emission computed tomography was used to detect glucose at a concentration of a nanomole with a high signal-to-noise ratio (SNR). Due to the low noise of the system, the gate current and its changes during glucose detection can be distinguished, but their research shows that the configuration of transistors does not improve the sensitivity of enzyme sensing. However, the use of transistors instead of passive electrodes significantly improved SNR, which proves that the application of the OECT in enzyme sensing is reasonable. Their research suggests that the technology of directly integrating electroactive elements into microfluidic channels may provide a novel approach for subsequent research in the field of microfluidic devices. The n-type OECT has a high SNR at the detection site and high sensitivity to low concentrations of glucose, making it more effective in the field of miniaturized biosensors. This will contribute to the application research of organic bioelectronics and microfluidics [42]. A continuous glucose detection system (CGM), a traditional portable glucose sensor, is an indispensable device in the daily life of diabetes patients [68]. Due to the current issues with such devices, such as pain during use, it is considered necessary to develop new devices [69]. In 2024, Bai et al. developed a new CGM based on the OECT. They used a microneedle array to extract samples to avoid pain, innovatively used interpenetrating polymer network (IPN)

hydrogel and added ferrocene amino as a medium to mediate the electrical transmission between GOx and OECT, and finally, obtained a CGM with adjustable sensitivity [70].

Moreover, there are many other metabolites that play a role in the human body, such as amino acids [50]; lactate [71]; troponin [53]; and urea [52]. In 2020, Zhang et al. fabricated an organic electrochemical transistor (OECT) modified with L-amino acid oxidase (L-AAODX) as a biosensor [50]. L-AAODX selectively catalyzes the oxidation of L-type amino acids such as L-tryptophan, L-tyrosine, and L-phenylalanine. For L-tryptophan, L-tyrosine, and L-phenylalanine, the sensor showed a sensitivity of 19.67 μA/μM, 16.71 μA/μM, and 15.51 μA/μM, respectively, with detection limits of 10 nM, 2 nM, and 10 nM, respectively. This sensor can specifically distinguish L-amino acids from their potential interferers (e.g., glutamic acid, uric acid, aspartic acid, lysine, etc.) and common metal ions (K^+, Na^+, and Fe^{3+}). In 2018, Anna et al. fabricated an N-type OECT sensor based on P-90 polymer films and realized the electrochemical detection of lactate by immobilizing lactate oxidase (LOx) on it [51]. In the same year, Currano et al. reported a flexible wearable sensor based on an OECT for the detection of lactic acid. By coating Pt electrodes with LOx immobilized in a notional glutaraldehyde matrix, the sensitivity of this sensor varies with LOx but still has high sensitivity at low lactate concentrations [71]. In 2020, Gualandi et al. reported a sensor for the detection of lactate and glucose. The specific detection of this sensor is achieved by modifying a mixture of lamellar double hydroxide (LDH) and GOx/LOx on a gold electrode [49]. In 2024, Neyra Recky et al. investigated the construction of a biosensor for urea detection by binding urease to PEDOT-PAH conductive polymer membranes through electrostatic integration and monitoring urease adsorption using Surface Plasmon Resonance analysis (SPR) and OECT techniques [52]. It is worth mentioning that polyallylamine (PAH) was used instead of PSS to construct the OECT.

Glycoproteins are proteins with oligosaccharide chains that are usually attached to the protein by glycosylation during post-translational modification [72]. The abnormal expression of glycoproteins is closely related to the occurrence and development of many diseases (such as cancer, cardiovascular disease, diabetes, etc.) and is widely used as an ideal biomarker for clinical diagnosis [73,74]. In 2024, Chen introduced a portable ultra-sensitive bioelectrochemical patch based on boronate-affinity amplified organic electrochemical transistors (BAAOECTs) and point-of-care (POC) for rapid on-site detection of glycoproteins [53]. Based on the specific interaction between phenylboronic acid (PBA) and a glycoprotein containing a cis-diol structure, they used a complex (BSA@PBA) formed by bovine serum albumin (BSA) bound to phenylboronic acid (PBA) to enhance the signal. Compared with commercial electrochemical luminescence (ECL) kits, its sensitivity, reliability, and correlation were greatly improved. With the global epidemic of COVID-19 infection, significant losses have already been caused. To achieve highly sensitive and rapid detection of COVID-19 antibodies, in 2021, Liu et al. formed a self-assembled mono-layer (SAM) on a gold electrode that immobilized SARS-CoV-2 spike proteins to the gate electrode to capture IgG antibodies and achieve rapid response [54].

Proteins can also enable specific detection of viruses. In recent years, the uncontrolled spread of coronavirus (COVID-19) disease has caused great losses worldwide, which calls for inexpensive, rapid, and highly sensitive test methods [75,76]. In 2023, Barra et al. developed an OECT-related sensor for detecting spike proteins associated with SARS-CoV-2 viruses by attaching anti-spike or anti-nuclear protein (anti-NP) antibodies to a gate. Then, these functionalized gates were incubated with different concentrations of spike Receptor Binding Domain (Spike-RBD) protein, and the electrical response to different protein concentrations was detected, which has the potential to be used as a biosensor [76].

3.2. Ion Sensing

Ionic sensing technology plays a crucial role in multiple key fields such as environmental monitoring [43,44], food safety [77,78], agricultural production [79], and biomedicine [80]. In the process of life, biologically related ions, such as K^+, Na^+, and Ca^{2+}, play a central role in nerve conduction, muscle function, and bone health [43]. In addition, ions, such as

H^+, participate in the acid-base balance of water environments, and their detection tools are called pH sensors, which are commonly used in environmental monitoring [81–83]. For a long time, traditional ion sensors have used electrochemical methods. This method relies on ion-selective electrodes (ISE) to measure the concentration of specific ions, which typically involves placing electrodes on both sides of an ion-selective membrane (ISM) and monitoring the potential difference generated between them. On the other hand, amperometry and conductivity methods are also widely used [84]. Nowadays, with the rise of OECT technology, the traditional ion-sensing method is undergoing innovative improvements and bringing unprecedented development opportunities for ion-sensing technology.

In 2014, Michele Sessolo's team developed an all-solid-state photoelectric current transformer using a gel electrolyte to achieve selective detection of potassium ions. This sensor is based on the traditional ISM on the gel electrolyte. PEDOT:PSS is used as the active channel material, which provides an integrated method by combining the typical ISM with the signal amplification provided by the photoelectric current transformer [85]. They demonstrated the universality of this structure in ion-selective sensors, achieving high sensitivity of the OECT without sacrificing selectivity. In 2018, Pierre et al. developed a simple circuit for indium-gallium-zinc oxide (IGZO) thin-film transistors (TFTs) for addressing and integrating multiple OECT sensors. They integrated IGZO TFTs with ion-selective OECTs (IS OECTs) on a flexible substrate to form an ion sensor array and read each sensor through a multiplexer [86]. In 2019, Scott T. Keene and his team deposited PEDOT:PSS on different ISMs to selectively sense calcium and ammonia ions in sweat while allowing skin contact [87]. They used an ISM to form an ion-insulated polyvinyl chloride matrix doped with replaceable ionization groups, which can selectively bind with ions and generate a transmembrane potential difference. To detect calcium ions, the ion carrier ETH129 was used, while non-actin was used for sensing NH^{4+} ions. In these two sensors, potassium tetrachlorophenylborate was spin-coated in a PEDOT blend solution to cover the ion carrier on the PEDOT:PSS layer in order to eliminate the influence of anions on the potential. Finally, the device was integrated onto a flexible substrate to obtain a wearable sensing patch. In 2022, Li et al. reported a class of performance enhancers tris (2-hydroxyethyl)-methylammonium methylsulfate ([MTEOA] [$MeOSO_3$]) for PEDOT:PSS. OECTs based on PEDOT:PSS/[MTEOA] [$MeOSO_3$] showed a high transconductance (22.3 $\pm$ 4.5 mS/μm), fast response time (40.57 μs), and excellent stability (retention rate > 95% after 5000 switching cycles). In addition, integrating the ISM with a finished OECT can result in selective ion sensors for detecting metal cations (Na+, K+), with a LOD of 0.75 mM for Na+ and 0.8 mM for K+, respectively [55].

Traditional pH sensors widely use glass electrodes [88]. However, due to the limitations of this material, these sensors have not made satisfactory progress in portability and miniaturization despite undergoing many developments [89,90]. Therefore, the common approach to applying OECTs to pH sensors is to modify the gate electrode or semiconductor channel of the OECT with pH-sensitive materials. Based on this method, many pH sensors based on OECTs have been developed [91–93]. In 2020, Mariani et al. designed and fabricated a portable pH sensor for detecting biological samples (Figure 3), which was made of a charge-conducting layer and a pH-sensitive layer based on PEDOT:BTB. The sensor achieved 62 mV/pH in the pH solution ranging from 2 to 7, and their work was a major breakthrough in portable pH sensors [94]. In 2024, Ma and his team developed an ultra-high sensitivity pH sensor based on vertical organic electrochemical transistors (vOECT) [56]. The sensor has an extended gate and is modified by electrochemical deposition of polyaniline (PANI). This pH sensor exhibits ultra-high sensitivity of 3363.6 μA/pH in the pH solution ranging from 5 to 9, making it the most sensitive transistor-based pH sensor reported to date. The research team electrochemically deposited PANI on the extended gate and optimized the scan rate using cyclic voltammetry (CV). The experimental results show that the pH sensor not only exhibits excellent reversibility, long-term stability, and selectivity but also demonstrates good performance in real sample testing.

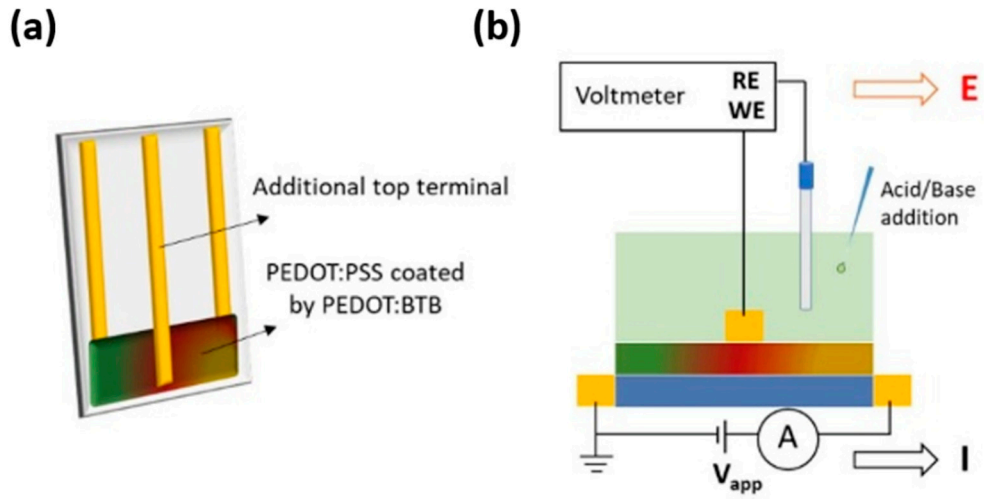

Figure 3. (**a**) Schematic diagram of electrochemical gating in pH sensor with additional gold orbitals in contact with sensing layer. (**b**) Experimental setup for studying sensing mechanism [94].

3.3. Neurotransmitter Sensors

Neurotransmitters, as the core endogenous chemical messengers of the nervous system, are key small molecules that regulate and transmit sensation and movement and integrate neuronal information. These small molecules are produced and released by the same neuron and stored in presynaptic terminals, inducing specific behaviors in postsynaptic neurons. Synapses are an important component of the nervous system, serving as the sensing and processing units required for signal transmission between neurons in the biological nervous system [95]. Meanwhile, their induction effect on postsynaptic cells can be terminated through specific mechanisms [96]. These neurotransmitters not only play crucial roles in various functions such as emotions, thoughts, memory, movement, and sleep patterns but also serve as fundamental regulators of neuronal growth, differentiation, and survival [97–100]. Abnormal levels of neurotransmitters can be reflected in brain dysfunction, leading to various physical, mental, and neurodegenerative diseases such as epilepsy [101,102]. These chemicals have a prominent impact on the nervous system, including acetylcholine, monoamines (such as dopamine, serotonin, and norepinephrine), amino acids (such as glutamate and gamma aminobutyric acid), and various peptides (such as enkephalins and substance P). These neurotransmitter categories have their own characteristics, such as acetylcholine, playing an important role in memory formation and muscle contraction [103]. Dopamine is involved in motor control, reward, and pleasure [104]. Serotonin is involved in regulating emotions and sleep [105]. Amino acid neurotransmitters affect our learning and cognitive abilities by regulating brain excitation and inhibition processes [106]. Peptide neurotransmitters are more involved in pain perception and emotional responses [107]. Through these different neurotransmitters and their complex interactions, our nervous system is able to finely regulate various physiological and psychological states, maintaining the dynamic balance of the body.

Dopamine (DA), as one of the most essential neurotransmitters in the human body, is closely related to numerous neurological diseases such as Alzheimer's disease, Parkinson's disease, and schizophrenia due to its metabolic imbalance. Therefore, developing a biosensor that can quickly and accurately detect dopamine levels is of great significance for achieving real-time diagnosis and timely treatment of these neurological symptoms [108–111]. Innovative methods have been used to prepare OECT-based biosensors without precious metal gate electrodes. Nafion and reduced graphene oxide-wrapped carbonized silk fabric (Nafion/rGO/CSF) have been used as gate electrodes, significantly improving the conductivity of the electrode and effectively avoiding the aggregation of rGO and Nafion. This biosensor has extremely high sensitivity and selectivity towards DA, with a detection limit of 1 nM and a wide detection range from 1 nM to 30 μM. In addition, the biosensor

can maintain good electrochemical sensing behavior even in a bent state and in artificial urine, demonstrating its enormous potential in flexible electronic products. The results indicate that carbon-based gate electrodes can also achieve high sensitivity comparable to noble metal gate electrodes, providing an unprecedented strategy for manufacturing high-performance and low-cost flexible OECT-based biosensors [57]. In the same year, a method was developed to regulate the sensitivity and selectivity of OECT-based biosensors through surface-engineered carbon cloth electrodes. Polyaniline-coated carbon cloth was used for carbonization at 750 °C to prepare nitrogen/oxygen co-doped carbon cloth (NOCC), and it was found that the carbonization process under different atmospheres can adjust the nitrogen and oxygen content and distribution on the surface of the NOCC electrode, thereby changing its electrochemical sensing behavior against ascorbic acid (AA) and DA. The experimental results show that the NOCC electrode prepared under a reducing atmosphere exhibits higher sensitivity to AA, while the electrode prepared under an oxidizing atmosphere has better selectivity for DA. In addition, through density functional theory (DFT) calculations, researchers further verified the effect of heteroatom doping on sensing behavior and found that N-6 and O-I atoms are not conducive to the adsorption and oxidation of AA on its surface but are more conducive to the detection of DA [45]. In 2022, a novel OECT-based biosensor was developed based on a molecularly imprinted polymer (MIP) modified gate electrode, which was utilized to detect dopamine. By electrochemically depositing a polypyrrole film on a platinum gate electrode and using DA as a template for peroxidation treatment, an OECT-based biosensor with high selectivity and sensitivity was successfully prepared. Research has shown that the biosensor exhibits good selectivity in the dopamine concentration range of approximately 0.4 to 10 μM, with a DA/AA signal ratio higher than 5. In addition, the biosensor also has the characteristics of low operating voltage and high transconductance, exhibiting excellent performance in aqueous environments [46]. In 2024, an OECT-based biosensor was developed based on a novel conjugated free radical polymer (BTMP-EDOT) and a traditional conjugated polymer, P3MEET. This biosensor is designed for detecting DA and demonstrates excellent sensitivity and selectivity. By precisely adjusting the mixing ratio of BTMP-EDOT and P3MEET, the performance of the OECT was optimized, with a maximum transconductance rate of approximately 400 mS. In addition, the design achieves excellent clinical-grade DA detection limits and significant specificity in the presence of a large number of interfering substances, and the biosensor can still detect the presence of dopamine at extremely low concentrations [112].

In addition, there are many reports on biosensors used for detecting triphosadenine (ATP), which is also a very important neurotransmitter. ATP is the most common small molecule in nature, closely related to various life activities in organisms. A number of studies have developed a series of biosensors using ATP as a detector [113,114]. In 2022, an organic photoelectrochemical transistor (OPECT) was developed based on OECT and photoelectrochemical analysis (PEC) technology. The working principle of this device is based on the mechanism of photo fuel generation and surface charge regulation. Unlike traditional OECT devices, this new type of device works under light conditions without the need for a continuous current. As shown in Figure 4, when CdS quantum dots are illuminated, their conduction band electrons and valence band holes migrate to the ITO electrode and ascorbic acid (AA) electrode, respectively, forming a current, which is equivalent to an additional positive voltage on the gate voltage V_G. This mechanism not only saves power supply but also allows the device to perform zero-bias operation without the need for external bias. In addition, ATP treatment triggers the dissociation of DNA superstructure, releasing some D2 and D3 fragments and reducing the negative charge density on the electrode surface. Due to the reduction in a negative charge, the surface potential and channel conductivity change, resulting in changes in the current response. This method can effectively avoid damage to the test object caused by current. Therefore, by controlling the surface charge, fine control of the OPECT system can be achieved (Figure 4) [115]. In 2023, an OECT based on PEDOT polyamine film was proposed for selective monitoring of

phosphate-containing compounds. Research has found that supramolecular monophosphate amino interactions can cause higher OECT response changes at low concentrations than ATP amino interactions. In addition, the effect of phosphate species on the assembly behavior of acetylcholinesterase (AchE) on PEDOT PAH OECTs was revealed through enzyme immobilization technology. As the phosphate concentration increased, enzyme anchoring decreased, and this biosensor could detect samples above 5 μM [116]. In 2024, an OPECT was developed based on a cascade DNA network structure for the sensitive detection of ATP. They achieved high-sensitivity detection of ATP by adjusting the surface potential of the ZnIn2S4/MXene Schottky junction and utilizing the amplification effect of the DNA network. The device demonstrated excellent performance with a detection limit of 0.3 pM [117].

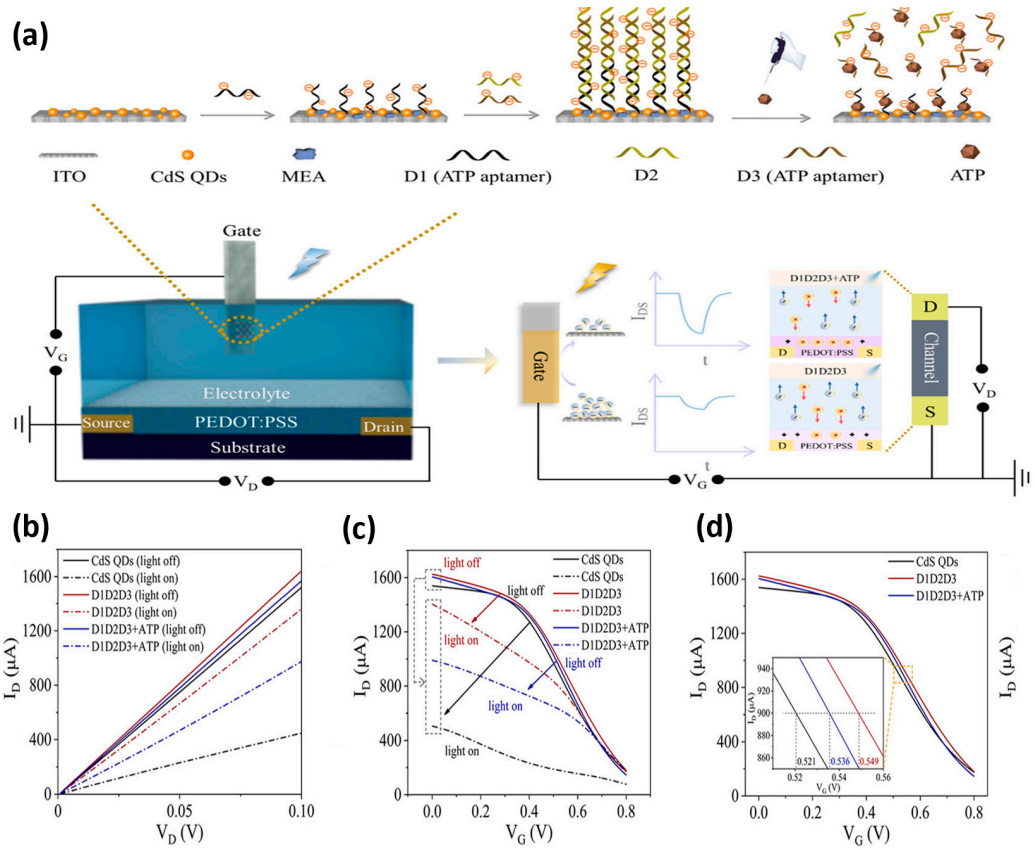

Figure 4. (**a**) Schematic diagram showing the structure and basic principle of organic photoelectrochemical transistor (OPECT)-based biosensors. (**b**) Output curves under different conditions. (**c**) Transfer curve under illumination conditions. (**d**) The transmission curve in the dark [115].

In summary, these studies demonstrate the sensitivity and selectivity of OECT-based biosensors in detecting neurotransmitters. Using different materials and methods, such as non-precious metal gate electrodes, surface-engineered carbon cloth electrodes, MIP-modified gate electrodes, and the application of novel conjugated polymers, researchers have not only improved the performance of biosensors but also reduced costs and enhanced their feasibility in practical applications. These developments are of great significance for promoting low-cost and high-performance OECT-based biosensor technology, especially in the fields of clinical diagnosis and personal health management.

3.4. Electrophysiological Signal Monitoring

The bioelectricity in the body is crucial for the functioning of nerves and muscles. This electrical activity is directly related to the physiological functions of the body and can be detected as an indicator of health status, which is also an important branch of bioelectronics technology in the medical field [118]. Long-term monitoring of electrophysiological signals such as an electrocardiogram (ECG) [47], electromyography (EMG) [119], and electroencephalography (EEG) [36] can provide rich physiological information, which can be used to monitor the body and diagnose and treat various diseases [120]. ECG readings are closely related to cardiac function and are commonly used to detect arrhythmias and cardiovascular diseases. EEG plays a crucial role in studying neurological disorders, including sleep status and epilepsy. EMG provides a deep understanding of muscle activity and is widely used for diagnostic evaluation of muscle function rehabilitation [121–123]. Traditional implantable sensors integrate electronic devices with the biological environment to successfully convert biological signals into clear and readable electrical signals without causing adverse effects within the biological system. Compared to traditional implantable potential sensors, the advantages of OECTs are obvious, which include (1) biocompatible materials—excellent biocompatibility makes the device safer without considering the impact of electrode materials on the human body; (2) equipment size; and (3) signal-to-noise ratio; among which the advantage of the signal-to-noise ratio is particularly prominent [33,124].

Traditional ECG monitoring is performed using electrodes located on the skin that help detect small electrical changes in the myocardium during each heartbeat (cardiac cycle), which can be observed in ECG in cases of cardiac abnormalities such as electrolyte imbalances or arrhythmia [125]. ECG can provide important information, such as the rate and rhythm of the heartbeat, the effects of cardiac drugs, the function of implantable pacemakers, and whether there is any damage to the cardiac muscle cells or conduction system, which are other measurable information [126]. Based on the application of OECTs in in vivo implantation, using bioabsorbable scaffolds as substrates is an effective method. This bioadsorption is beneficial for implanted devices and eliminates the need to remove them. In this case, both organic and inorganic materials can be used to manufacture electronic devices composed of components that are soluble after degradation and produce non-toxic fragments at fixed time intervals [127–129]. Campana et al. proposed a novel manufacturing process in 2014 (Figure 5), a technique for building OECTs on poly (L-lactide-co-glycolide) (PLGA). They prepared 20 μm thick uniform and transparent PLGA substrates with an average roughness strictly controlled within 2 μm. Evaporate and deposit a 30 nm gold layer on the PLGA thin film, and form source and drain electrodes through a shadow mask. Spin coat PEDOT:PSS onto the substrate and perform thermal annealing at 50 °C to form a layer approximately 200 nanometers thick. To avoid hydrolysis and delamination, it is necessary to ensure the pH neutrality of PEDOT:PSS suspension. Pattern PEDOT:PSS through a dry etching process to protect the transistor area from etching effects. Finally, the stability and high sensitivity of the device under low voltage operation were verified by testing its performance in an aqueous phosphate buffer solution. The final product is shown in Figure 5b. Subsequently, the author directly connected the exposed polymer channels of the OECT to the skin for human ECG recording. As with traditional ECG recording methods, conductive gel is used to help adhesion and reduce skin resistance. In this way, the skin acts as the gate electrode, and the potential of the skin changes according to grounding, resulting in instantaneous changes in I_D. The results showed that the SNR was comparable to the traditional potential recording of Faraday electrodes [47]. In 2022, Li et al. reported the application of tris (2-hydroxyethyl)-methylammonium methylsulfate ([MTEOA] [$MeOSO_3$]) as an additive to PEDOT:PSS. They applied a device based on flexible substrates for ECG signal detection and obtained high-quality signals [55].

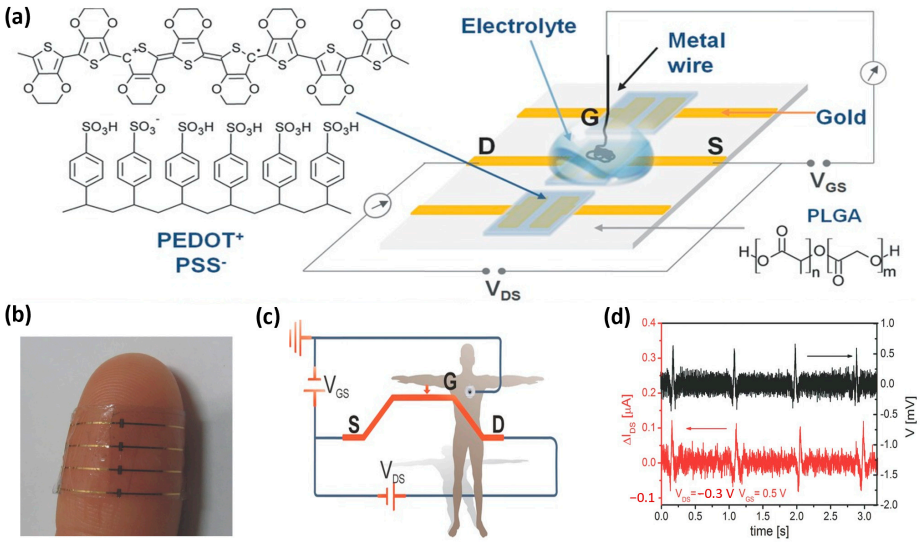

Figure 5. (**a**) Schematic diagram of the structure of the OECT-based biosensor. PEDOT:PSS is patterned as an active layer on a bioabsorbable PLGA film, in contact with the gold source and drain electrodes. This structure is gate-controlled by the electron potential applied to the aqueous electrolyte through a metal wire. (**b**) The photo of the device shows the transparency and flexibility attached to human skin. (**c**) Experimental wiring diagram. (**d**) The drain current trace (red) measured during electrocardiogram recording (V_{SG} = 0.5 V, V_{SD} = −0.3 V) was compared with the normal potential record using standard disposable leads (black) [47].

3.5. Other Sensor Applications

With the progress of modern civilization promoting more human-to-human or animal-to-human contact, infectious diseases are more likely to spread rapidly through various contacts that cause pathogens to enter the human body, such as influenza, SARS-CoV-2, Ebola virus, etc. [130]. These infectious diseases pose a huge threat to humans. Tang et al. developed a Functional Infectious Nanoparticle Detector (FIND) based on OECT and electrochemical impedance spectroscopy (EIS) in 2021 [131]. They combined influenza virus H3N2 with organic bioelectronic devices, formed Supported Lipid Bilayers (SLBs) on PEDOT:PSS substrates, and confirmed the fusion of the virus with the host cell membrane using optical technology. Then, the electrical signal changes caused by virus fusion were detected using OECT and EIS techniques. In the same year, Butina et al. reported an OECT-based biosensor for detecting Salmonella [132].

Cytokines are an important class of small molecule proteins involved in human immune function, and their production is influenced by environmental stimuli, stress, or diseases [133]. In 2023, Chiara Diacci and his team developed only one OECT-based biosensor for interleukin-6 (IL-6), which is a planar OECT device fabricated using photolithography technology on polyethylene naphthalate (PEN) foil. They used the specific sequence to functionalize the surface of the OECT for selective IL-6-specific recognition, and in their study, Tumor Necrosis Factor (TNF) was used as a control for specific detection [58,134]. In the experiment, $HAuCl_4$ was electrochemically deposited on PEDOT:PSS film to modify the gate electrode, forming an AuNP/PEDOT:PSS structure, and then the aptamer was fixed on the AuNP by electrochemical reduction. This modification method can improve the modulation effect of the channel, increase conductivity, and have fast transmission characteristic stability. In addition, using 6-mercapto-1-hexanol (MCH) molecules as protective groups for aptamers, an anti-fouling layer can be formed on the sensing surface, further improving stability. Through EIS analysis, it can be observed that the binding of aptamers and MCH to the surface of AuNP/PEDOT:PSS forms a barrier layer against negative charges, thereby increasing the charge transfer resistance (R_{ct}). Experimental results have shown that this OECT-based aptasensor has good stability.

Water quality is an important environmental issue facing the world today. The natural water sources that humans come into contact with in their daily lives are also one of the important factors affecting human health and well-being. Therefore, detecting pathogens, microorganisms, and elemental components in water quality is particularly important. In 2014, an ocean biosensor was designed based on an OECT for detecting marine diatoms in seawater [48]. Diatoms are photosynthetic algae composed of siliceous skeletons and are found in almost all aquatic environments. But diatoms are easy to attach to solid surfaces, and their attachment forms a diatom biofilm, attracting many other marine organisms to attach. The attachment of marine organisms to ship hulls can lead to many problems, including increased energy consumption, higher maintenance costs, and higher corrosion rates. The principle of this diatom biosensor is similar to most OECT-based biosensors used for detecting DNA. During the detection process, when diatoms adhere to the PEDOT:PSS layer of the OECT due to the electrostatic interaction between them, the battery will apply additional voltage on the OECT, requiring a higher gate voltage to compensate for the excess negative charge. Therefore, the more diatom cells attached, the higher the observed offset voltage, which can also be attributed to the static interaction between diatoms and the PEDOT:PSS layer. The reported device detected two common marine diatoms, namely the genus Synechococcus and the genus Synechococcus. This study was conducted in an artificial seawater environment, where diatom detection can still be distinguished from OECT biosensor transmission curve data, indicating the potential for actual seawater detection in marine diatom detection.

Circulating tumor cells (CTCs) are specialized cells that are shed from the primary tumor and enter the circulatory system. They have a strong ability to migrate and proliferate, and most tumor metastases are closely related to CTCs; therefore, CTCs are considered potential tumor biomarkers in liquid biopsy [135]. CTCs can be detected in peripheral blood even in the early stages of cancer, making their detection useful for cancer diagnosis, therapeutic efficacy, and prognosis. In 2019, Yeung et al. cocultured NPC43 cells with epithelial cells on a 4×4 16-channel OECT platform and recorded the electrical response of the OECT platform. Using multi-channel recordings, they were able to distinguish NPC43 from other epithelial or cancer cells (e.g., Caco-2; MDCK; NP460) and formed a non-optical spatial mapping [136]. In 2023, Song et al. designed a sensor that introduced an anti-EpCAM antibody onto the PEDOT:PSS conductive membrane and realized the detection of MCF-7 cells [137]. They increased the surface hydroxyl group of the PEDOT:PSS layer by plasma treatment in order to immobilize the anti-EpCAM antibody to the OECT channel surface by silane. They verified that this sensor could enable the identification of different numbers of cancer cells.

Highly sensitive and accurate DNA detection methods are essential for medical diagnosis by conventional laboratory methods, such as fluorescent labeling [138], have shown high sensitivity and accuracy, but these methods are costly [139]. Therefore, the use of OECTs is valued as an inexpensive and highly sensitive method. In 2021, Chen et al. developed a DNA detection method by combining OECT and nucleic acid self-assembly signal amplification [60], hybridization chain reaction (HCR) occurred on the Au electrode to form long-stranded double-stranded DNA, and the voltage difference on the electrode was realized to complete the DNA detection.

4. Conclusions

Research on OECT-based biosensors has increased in recent decades, mainly due to their characteristics of local signal amplification, enhanced SNR, high sensitivity, and biocompatibility. By using OMIEC materials as conductive channel materials, selectivity, biocompatibility, and flexibility are provided, and these properties are further enhanced. Meanwhile, wearable medical devices have become a popular research direction for biosensors in recent years. Biosensors based on OECTs also have extremely high versatility, as demonstrated by their applications in metabolite detection, ion detection, and environmen-

tal monitoring. The foreseeable future is that as more alternative OMIEC materials are developed, research in this field will enter the next thriving new stage.

Although significant progress has been achieved in the field of OECT-based biosensors, there are still face challenges for the sake of practical applications. For example, one of the problems that needs to be overcome is the integration of semiconductors and biological entities, namely the dependence of OECTs on PEDOT:PSS materials. Currently, most OECT-based biosensors are built on this OMIEC basis. However, this material has significant defects, such as the lack of functional groups in the original PEDOT membrane, which greatly hinders the integration of OECTs with biological entities [140,141]. Meanwhile, excessive PSS in PEDOT:PSS leads to negatively charged surfaces, which limits their interactions with most proteins, nucleic acids, and cells [142], thus causing many challenges in practical applications. This issue can also be seen as a breakthrough in sensor performance, and in recent years, research has not only explored traditional biological binding but also modified OECTs. This is evident in the emergence and application of OEPCTs [115,116] and the exploration of OMIECs that can replace PEDOT:PSS, such as PEDOT-PAH [116]. Efforts have explored a new bright future for this research direction. But we cannot be satisfied with the current situation. From this perspective, breakthroughs in materials science are necessary, and at the same time, continuous in-depth exploration and efforts are needed for the existing types of OECT-based biosensors. In this review, the optimization of channel materials, innovation of sensor structures, and differences in usage environments are presented. It could potentially lay the foundation for the flourishing development and clinical popularization of OECT-based biosensors.

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