Organic thin film transistors-based biosensors

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Abstract
Organic thin film transistors (OTFTs)-based biosensors are widely applied as advanced biosensing platforms by virtue of their inherent ability to transfer and amplify received biological signals into electrical signals. Nevertheless, the development of OTFTs-based biosensors with excellent sensitivity, selectivity, and stability for specific biological processes remains a major challenge. This mini review focuses on recent achievements in OTFTs-based biosensors since 2010. Specifically, three types of OTFTs, specifically organic field-effect transistors (OFETs), electrolyte-gated OFETs (EGOFETs), and organic electrochemical transistors (OECTs) are summarized in terms of the key strategies required for high-performance bioelectronics. Additionally, various OTFTs-based biosensors, such as ions, glucose, nucleic acids, proteins, and cells are described in terms of their working principles. This mini review highlights the uses of OTFTs for a broad range of research applications with a focus on designing novel OTFTs-based biosensors.

KEYWORDS
biosensors, electrolyte-gated organic transistors, organic bioelectronics, organic electrochemical transistors, organic field-effect transistors, organic thin film transistors

1 | INTRODUCTION
In recent years, effective communications between biological signals and electrical signals have been enhanced through organic bioelectronic devices, which are mainly divided into two categories: bioelectronic devices used to detect target biomolecules and biological signals,1-3 and bioelectronic devices that imitate biological functions to prepare artificial electronic devices.4,5 Although their functions are different, both types of device have certain material requirements in terms of stability and biocompatibility.6 The biocompatibility of organic thin film transistor (OTFT) materials is nothing but the compatibility of OTFT materials with biological system. The assessment is mainly through a series of experiments in vivo and in vitro to see if there is a toxic effect on biological system. Specifically, whether cell proliferation and cell differentiation are affected, and whether inflammation is induced through the interaction with OTFT materials. Over the years, it is anticipated that polymer OTFT
materials possessed the required features, in particular, they are mechanically and flexibly tunable that influences the construction of stretchable bioelectronics with improved tissue contact to the implantable device surfaces. From the perspective of organic semiconductors (OSCs), π-conjugated OSCs have similar chemical structures to various biological substances and thus have excellent biocompatibility. In addition, weak interactions between OSCs and external substances with noncovalent bonds guarantee stable sensing of chemical, biological, and physical parameters. Moreover, OSCs are rich in variety and easy to tailor or modify, which is attractive for molecular design to achieve specific recognition of analytes. From the perspective of the OTFTs, OSC layer, dielectric layer, gate electrode, and other functional layer have been used as sensing sites, which make various OTFTs-based biosensors. Moreover, by changing multiple electrical output parameters, such as mobility (μ), threshold voltage (Vth), on/off ratio (Ion/Ioff), source-drain current (Id), and subthreshold slope (SS), OTFTs-based biosensors can efficiently transfer and amplify detected biological signals into electrical signals. Compared with their inorganic counterparts, OTFTs-based biosensors are fabricated with large-area through solution-processable techniques at low temperature, enabling the integration of devices with good compatibility and flexible substrates. Relative to traditional biosensors, OTFTs-based biosensors are an essential platform for facile and effective biosensing applications with shorter analysis time as well as lesser sample volume. However, the sensitivity, selectivity, and stability of OTFTs for biosensing applications still require further improvement. In this mini review, recent state-of-the-art developments of OTFTs are presented for various biosensing applications. First, we introduce the structure and operational mechanisms of OTFTs, before outlining several strategies for their fabrication and functionalization to obtain high-performance OTFTs-based biosensors. Subsequently, we discuss the applications of these biosensors for various analytes, such as ions, glucose, nucleic acids, proteins, and cells. Besides, we describe approaches using a range of biosensors, including organic field-effect transistors (OFETs), electrolyte-gated OFETs (EOGFTs), and organic electrochemical transistors (OECTs). Finally, we consider the perspectives of OTFTs-based biosensors in broader analytical and clinical applications.

2 | THE STRUCTURE AND OPERATIONAL MECHANISM OF OTFTS

Before presenting a detailed discussion of OTFTs-based biosensors, herein we provide a concise introduction to OTFTs. In general, OTFTs are three-terminal electronic devices with four different types of structures, as shown in Figure 1. Their operational mechanism can be explained as follows. When a gate voltage (Vg) is applied, carriers are induced at the interface between the OSC layer and dielectric layer, forming a conductive channel. Subsequently, carriers are injected from the source electrode to the drain electrode under the source-drain voltage (Vds). To evaluate the performance of OTFTs, several parameters, including μ, Ion/Ioff, and Vth are calculated via transfer and output curves. Among these parameters, μ is extracted through transfer curve in either the linear regime (Ids = WμC(Vg - Vth)/L) or the saturation regime (Ids = WμC(Vg - Vth)2/2 L). Ion/Ioff and Vth are responsible for switching behaviors of OTFTs. The desired higher Ion/Ioff and lower Vth enable the device to operate more effectively in practical applications. Rapid developments in manufacturing technologies and OSC materials have further improved the performance of OTFTs. Numerous OSC materials with chemical structures similar to various biological molecules have attracted great attention in bioelectronics applications. For example, small molecule OSCs such as pentacene, (trisopropylsilylthienyl)-pentacene, dinaphtho[2,3-b:2',3'-f]thieno[3,2-b]thiophene (DTNT), 2,9-didecyl-dinaphtho[2,3-b:2',3'-f]-thieno[3,2-b]thiophene (C10-DNTT), 2,7-dioctyl benzothieno[3,2-b]benzothiophene, 2,6-diphenylanthracene (DPA), 2,6-di(2-naphthyl)anthracene (DNA), naphthalene diimide, and perylene tetracarboxylic diimides have been used to fabricate high-quality OTFTs via various methods. However, the performance of most small molecule OSCs degrades rapidly when exposed to moisture. In order to further improve their stability, polymer OSCs such as poly(3-hexylthiophene) (P3HT), poly[2,5-bis(3-tetradecylthiophen-2-yl)thieno[3,2-b]thiophene] (PBT), π-conjugated donor-acceptor copolymers, as well as P(NDI2HD-T2Cl2) and P(NDI2OD-T2Cl2) have been produced to exhibit better solution processibility and film-forming properties. Commonly used OSC materials are listed in Figure 2. It is important to note that the performance of OTFTs depends not only limited on the film properties of the OSC materials, but also on the nature of the interfaces between the electrode/OSC, dielectric/OSC, and atmosphere/OSC. Recently, several approaches have been proposed to obtain high-performance OTFTs. A common strategy is the doping method. Through introducing dopants into OSC materials, the charge injection barrier and carrier concentration can be regulated precisely; therefore, it can enhance μ, adjust Vth, passivate trap states, and improve stability. The insertion of a high ionization energy interlayer between the electrodes and the OSC layer is also a critical
**FIGURE 1** Four configurations of organic thin film transistors (OTFTs). A, Top gate top contact type (TGTC). B, Top gate bottom contact type (TGBC). C, Bottom gate bottom contact type (BGBC). D, Bottom gate top contact type (BGTC).

**FIGURE 2** Chemical structures of organic semiconductors (OSCs) discussed in this review; left panel shows organic small molecule semiconductors and right panel shows organic polymer semiconductors.
strategy. A third approach depends on solvent engineering. For example, through addition a low amount of “bad” solvent (acetone) in the “good” solvent (chloroform) of the polymer, a threefold increase in OTFTS transconductance is achieved due to the increased electron mobility ($\mu$) and volumetric capacitance ($C^*$) in the channel. Moreover, polymer/dielectric blends and metal-chelating conjugated polymer OSCs are also used to enhance and modulate the charge transport properties of OTFTs. By blending polystyrene (PS) with DPP-based polymer OSCs, hole mobility is increased three times and the morphology of the fiber network is significantly modified. Interestingly, by incorporating metal-chelating moieties, such as Fe to OSCs, charge transport properties can also be enhanced and modulated without the need for multistep synthesis. Consequently, high-performance biosensor-based OTFTs have been widely developed and applied in numerous sensing applications.

3 | THE OVERVIEW OF OTFTS-BASED BIOSENSORS

A typical OTFTs-based biosensor is an organic bio-electronic device composed of OTFTs and active biomaterials to transduce biological events into electrical signals. The working principle of OTFTs-based biosensors requires that a specific biological event changes the carrier injection and transmission properties in the OTFTs via various interactions, including hydrogen bonds, charge transfer, dipole-dipole interaction, and so forth. Therefore, the quantitative signals conversion is realized by OTFTs-based biosensors.

When compared with traditional biosensors based on bulky and expensive equipment with lengthy operation procedures, OTFTs-based biosensors have numerous benefits, particularly for label-free, low-cost, portable, and real-time diagnostic applications. OFETs, EGOFTs, and OECTs are three common types of OTFTs applied in the field of biosensors. OFETs and EGOFTs are based on the modulation of the carrier density in the channel due to the electric field from the gate electrode. Specifically, when the OSC layer is exposed to target analytes, the biological event induces changes in output parameters such as $V_{th}$ or $I_{ds}$ via doping or trapping processes within the channel. OECTs are based on ion injection from the electrolyte solution into bulk OSC materials by electrochemical doping and dedoping processes. The target analytes in the electrolyte solution are thus selectively detected through appropriate functionalization on either the OSC layer or gate electrode. More details are presented in the following.

3.1 | OFETs-based Biosensors

Recently, the OFETs-based biosensors have been increasingly applied in health-monitoring and information technologies, such as pulse oximeters, temperature/pressure signals, electrocardiographic (ECG) recordings, and electrophysiology arrays. Despite the wide applications of these biosensors, the degradation of OSCs following exposure to moisture is among their major limitations. Hereupon, to mitigate this challenge, an extended-gate OFET is employed to prevent degradation by separating the extended-gate electrode (sensing area) from the OFET (driving unit). The “extended-gate” means that a part of gate area is separated from the traditional OTFT. When it works, the gate in traditional OTFTs will be influenced by a specific biological event appearing at the extending gate, and therefore the electric output properties of OTFTs will also be further impacted. For instance, a sensitive OFET-based C-reactive protein (CRP) biosensor with a limit of detection down to 1-$\mu$g/mL is depicted in Figure 3A by utilizing an extended-gate electrode immobilized with CRP antibodies. The functionalized electrodes effectively modulate the gate bias by regulating its surface potential to a specific combination of antibodies and antigens. Besides that, an extended-gate OFET-based enzymatic biosensor capable of selective nitrate detection is shown in Figure 3B for selective nitrate detection. Its mechanism relies on a specific combination of nitrate and nitrate reductase at the extended-gate electrode, which further influences the electric properties of OFETs. The aforementioned OFET-based biosensors with extended-gate electrodes guarantee stable detection of analytes in aqueous media. However, additional reference electrodes are needed in their fabrication process, resulting in a more complicated method of determination. To solve this problem, a novel label-free OFET-based protein biosensor (Figure 3C) has been developed with no reference electrodes, thereby substantially simplifying the sensing system and improving the performance of the biosensor.

High operational voltage is another limiting factor and might contribute to unstable electrical signal outputs. To prevent this, various charge storage layers have been used to develop low-voltage ($\sim$2 V) OFET memory devices, as shown in Figure 3D. By incorporating [6,6]-phenyl-C$_{61}$-butyric acid methyl ester into polyimide (PI), an interfacial charge storage layer is formed between pentacene and the PI, which guarantees efficient carrier programming and low-voltage operation. Furthermore, appropriate dielectric crystals, such as AlN shown in Figure 3E,F, can decrease the prevalence of defects and charge traps in the channel, resulting in high-performance OFET devices with low-voltage operation. Most recently, a bilayer-type
dielectric configuration,\textsuperscript{52} in which the low-k polymer is modified on a high-k fluoropolymer as a buffer layer, has been employed (Figure 3G). Results obtained by using this fluoropolymer denote that the OFETs-based biosensors with low-voltage and stability increase the sensing capabilities of analyte determination. Moreover, silk
fibroin is used as the gate dielectric in the fabrication of flexible OFETs as shown in Figure 3H, and the measurement stability in solution at low-voltage operation is greatly improved.

3.2 EGOFETs-based biosensors

Unlike the OFET structures described above, the OSC layer and gate electrode of EGOFETs are separated by an electrolyte solution. Having electric double layers (EDLs) established at the interface of the electrolyte/gate and electrolyte/OSC, both the gate electrode and OSC layer can serve as sensing areas with specific receptors. Gate functionalization usually uses thiol-gold chemistry to assure well-established EGOFETs through self-assembled monolayers (SAMs) of thiolates on the gold gate electrode. For example, an EGOFET-based dopamine biosensor with a layer of SAMs on the gate electrode is described in Figure 4A. According to the induced surface dipole potential, both shifts of the electrode work function and changes in its double layer capacitance can be used as sensing signals for selective dopamine determination. From the point of view of functionalization on OSC layer, modification with functional groups may be performed to covalently anchor biomolecules through various surface modification with functional groups. Gate functionalization usually uses thiol-gold chemistry to assure well-established EGOFETs through self-assembled monolayers (SAMs) of thiolates on the gold gate electrode. For example, an EGOFET-based dopamine biosensor with a layer of SAMs on the gate electrode is described in Figure 4A. According to the induced surface dipole potential, both shifts of the electrode work function and changes in its double layer capacitance can be used as sensing signals for selective dopamine determination. From the point of view of functionalization on OSC layer, modification with functional groups may be performed to covalently anchor biomolecules through various surface treatment strategies. Magliulo et al introduced an ultrathin carboxylic acid-modified functional layer on an EGOFET-based biosensor as shown in Figure 4B. Thereafter, sensitive and selective DNA determination is conducted via carbodiimide (EDC) and succinimide (NHS) activation. In addition, Shen et al tailored a molecular antenna on the surface of the OSC layer as an approach to detect adenosine triphosphate (ATP), as indicated in Figure 4C. This mechanism relies on the fact that both hydrolysis and the binding process of ATP affect the amount of positive charge and lead the shift of \( V_{th} \). Besides, Mulla et al presented a simple method to modify functional groups on the OSC surface by UV irradiation cross-linking polyacrylic acid (PAA) (Figure 4D). This enables covalent immobilization with sensitive probes for nM level determination of the target streptavidin (SA) molecules. Although the above methods ensure robust and stable biological detection, the degradation of OSCs and denaturation of biomolecules are enduring challenges. To mitigate these effects, a relative facial and fast modification process through physical adsorption is highly desired. For example, a label-free EGOFETs-based procalcitonin (PCT) biosensor is developed in Figure 4E. Incorporating antibodies specific to PCT biomolecules immobilized on the OSC layer by direct physical adsorption, the entirety of the fabrication and selective determination processes may be conducted in 45 minutes.

Charge-screening effects occur in charge-sensitive devices such as EGOFETs when the length of the charged biomolecules in high ionic strength solutions exceed the Debye length \( \lambda_D \). To reduce charge-screening effects, water-gated OFETs are utilized instead of EGOFETs in order to improve the sensitivity of OTFTs-based biosensors with \( \lambda_D = 206 \text{ nm} \), that is, much longer than most charged biomolecules. To further improve operational stability in solution, \( \pi \)-conjugated donor-acceptor copolymers have been extensively used for many high-performance OTFTs-based biosensors. Understanding carrier transportation properties between the OSC layer and the water interface is also important for designing high-performance water-gated OFETs-based biosensors. In this regard, the charge carrier transportation at the interface between the OSC layer and water was studied by Zhang et al, the results of which give suggestions for material selection and interface design in biomedical applications. Besides, Sun et al developed a water-gated OFETs-based alpha-fetoprotein (AFP) biosensor as a label-free general sensing platform for early liver cancer diagnosis (Figure 5A). The mechanism can be stated as follows: when negatively charged antibodies are absorbed onto the OSC layer, more hole carriers are induced in the channel, causing \( V_{th} \) to shift in the positive direction. The results shown in Figure 5B demonstrate that concentration dependence ranges from 1 ng/mL to 1-µg/mL with a limit of detection of 0.15 ng/mL. In order to further explore this mechanism, PBTTT and P3HT-based OTFTs are fabricated as shown in Figure 5C for the determination of picric acid (PA). These results demonstrate the action of two operational modes. The first is an OFET mode focusing on established EDLs at the electrolyte/gate and electrolyte/OSC interfaces, the latter part of which guarantees the electric field-effect transportation with ions in the water and opposed charge carriers at the OSC surface. The second is an OECT mode focusing on injected ions from the electrolyte/OSC interface to the bulk of the OSC layer, leading to doping/dedoping effect. Irrespective of the operational mode, the mechanism is dependent on changes in the mobile charge carrier density and shifts of \( V_{th} \) contributing to additional charges or trapping states due to the biomolecules. For sensing applications, the lack of specific binding sites on the OSC layer limits its further application with high sensitivity and selectivity. To address these issues, Suspene et al developed biotin-functionalized water-gated OTFTs-based avidin and SA biosensors with biotinylated polymer (P3HT-biotin) as the active OSC material, as shown in Figure 5D,E. Through peptidic coupling, variation in \( I_{ds} \) and a shift of \( V_{th} \) were observed during interactions between avidin and SA biomolecules. Furthermore, Kergoat et al described a water-gated OTFTs-based...
FIGURE 4  A, Structural diagram of organic field-effect transistors (OFETs) with a self-assembled monolayer (SAM); (a) with poly(dimethylsiloxane) pool to confine phosphate buffer solution (PBS); (b) with cysteamine (No. 1), 4-formylphenyl boronic (No. 2), and dopamine (No. 3) making up the steps of SAM; (c) the operating state of the device. Reproduced with permission from Reference 54. Copyright 2012, Elsevier. B, Structural diagrams of previously proposed OFETs-based biosensors: (a) OFETs-based biosensor with bilayer; (b) OFETs-based biosensor with functional biological interlayer (FBI); (c) electrolyte-gated OFETs (EGOFETs)-based biosensor; (d) preparation diagram for phospholipid BIOEGOFETs; (e) Output curves and gate current-voltage characteristic curves of BIOEGOFETs in the presence of PBS. Reproduced with permission from Reference 56. Copyright 2013, John Wiley and Sons. C, Structural diagram showing the PIMIG method applied to O2 plasma in order to introduce binding functional groups. Enzymes are immobilized on organic semiconductors (OSCs) via cross-linkers. Reproduced with permission from Reference 57. Copyright 2018, Royal Society of Chemistry. D, Structural diagram showing the preparation process of EGOFETs-based biosensors. The first step requires the deposition of OSCs on the surface of a silica substrate. (a) Poly(acrylic acid) (PAA) is immobilized on the OSC layer by spin-coating technology and is cross-linked under UV irradiation (254 nm); (b,c) bioprobes of biotinylated phospholipids are immobilized on PAA layer by carbodiimide (EDC)/succinimide (NHS) amine chemical coupling; (d) electrical and sensing tests are carried out on EGOFETs containing a droplet of PBS as the electrolyte and gold as the gate electrode. Reproduced with permission from Reference 58. Copyright 2015, Royal Society of Chemistry. E, Diagram of EGOFETs-based biosensors designed for PCT sensing. First, anti-PCT is physically adsorbed on the surface of the polymer poly(3-hexylthiophene) (P3HT) (No. 1), then bovine serum albumin (BSA) is added to block nonspecific protein binding (No. 2). Finally, the constructed immunosensor is exposed to the analyte PCT to detect electrical signals (No. 3). Reproduced with permission from Reference 59. Copyright 2017, Elsevier.
DNA biosensor in Figure 5F with arboxyl-terminal P3HT to achieve covalent grafting via NHS/EDC chemistry. Figure 5G showed the clear changes of electrical characteristics exhibited upon DNA hybridization, in which and the negative $V_g$ shift is caused by negative charges in the DNA backbone.
3.3 | OECTs-based biosensors

Compared with the OFETs and EGOFETs-based biosensors, OECTs provide a higher transconductance through strong ionic/electronic interactions between ions in the electrolyte solution and the bulk of OSCs through doping and dedoping effect. Additionally, OECTs-based biosensor arrays with a much lower operational voltage and simple device structure are achieved for facial, label-free, real-time, and high throughput chemical and biological sensing. To fabricate the desired OECTs, polythiophene doped polystyrene sulfonate (PEDOT: PSS) is widely used as excellent candidate materials for the active OSCs layer via spin-coating or inkjet printing processes. Through doping strategy, the conductivity of the PEDOT: PSS polymer increases greatly, and exhibits more excellent stability for solution method. The addition of poly(vinyl alcohol) (PVA) or poly(ethylene glycol) (PEG) to the bio-functionalized PEDOT: PSS for specific biomolecule determination is widely used in biomedical devices. For instance, Strakosas et al. demonstrated a simple and convenient process for sensing and biofunctionalization relying on the addition of PVA to facilitate covalent connections between biomolecules and PEDOT: PSS films. These protein biomolecules will not survive denaturation, because the harsh processing conditions (high temperature and solvents) are treated before biomolecules immobilization. After PVA incorporation, no decrease in the performance of ionic transport properties will occur. Furthermore, by virtue of their excellent biocompatibility, PEDOT: PSS is widely utilized for biosensing. Cui et al. synthesized a novel OECTs functionalized with PEG polymers are also widely used as excellent candidate materials for the active OSCs layer via spin-coating or inkjet printing processes. Through doping strategy, the conductivity of the PEDOT: PSS polymer increases greatly, and exhibits more excellent stability for solution method. The addition of poly(vinyl alcohol) (PVA) or poly(ethylene glycol) (PEG) to the bio-functionalized PEDOT: PSS for specific biomolecule determination is widely used in biomedical devices. For instance, Strakosas et al. demonstrated a simple and convenient process for sensing and biofunctionalization relying on the addition of PVA to facilitate covalent connections between biomolecules and PEDOT: PSS films. These protein biomolecules will not survive denaturation, because the harsh processing conditions (high temperature and solvents) are treated before biomolecules immobilization. After PVA incorporation, no decrease in the performance of ionic transport properties will occur. Furthermore, by virtue of their excellent biocompatibility, PEDOT: PSS is widely utilized for biosensing. Cui et al. synthesized a novel OECTs functionalized with thiol groups on the active layer of the device via electrochemical polymerization of PEDOT and PEG. Subsequently, various biomolecules, such as antibodies, were immobilized onto a PEDOT/PEG composite using gold nanoparticles (AuNPs), enabling the determination of target biomarkers. These strategies allowed an ultrasensitive OECTs-based immunoglobulin G biosensor printed on plastic substrates to be developed with attomolar detection limits. Such work emphasizes that plastic OECTs-based biosensors have wide applications in facial, noninvasive, ultrasensitive immunoassay biotechnologies. With the exception of biomolecules determination, recording bioelectric signals has also attracted considerable research attention. A bioelectric recording OECTs-based on PEDOT: PSS has been applied in electrocardiography (Figure 6A,B), highlighting the feasibility of OECT devices for monitoring health by recording ECG signals. In addition, high-resolution, ultraflexible ECG arrays composed of OECTs and OFETs have been fabricated as shown in Figure 6C to measure myoelectric signals using blue light stimulation. Subsequently, for convenient wearable healthcare monitoring, a flexible and stretchable OECTs-based fabric biosensor has been successfully fabricated with cotton yarns in Figure 6D. In summary, OTFTs are promising platforms for in vitro and in vivo sensing applications by virtue of their high biocompatibility and long-term stability.

4 | APPLICATIONS OF OTFTS-BASED BIOSENSORS

Since the bioelectric phenomenon was discovered by Galvani in the eighteenth century, organic biological devices have found deep connections between biological systems and OTFTs through transducing biological events into electrical signals. The OTFTs can not only achieve efficient ion-electron exchange and transfer via hydrated ions injecting into the bulk OSCs materials, but also display a greater stability and conformability with biological systems. Harnessing their inherent amplification functions and intrinsic biocompatibility, OTFTs-based biosensors have been widely used in monitoring cell activities and in the recognition of specific biomolecules. Further details concerning recent advances in OTFTs-based biosensors are presented in the following.

4.1 | OTFTs-based ion biosensors

OTFTs-based pH and ion biosensors have been widely developed because OSCs are sensitive to ion-doping. For example, OTFT-based pH sensors have been successfully fabricated with pentacene OSC layers as shown in Figure 7A,B. Changes of output electrical signals contribute to charge carrier variation, which is itself modulated by the pH value at the dielectric/electrolyte interface. Charge variation at the dielectric/electrolyte interface induces the redistribution of charges in the OSC layer, which is directly determined via OTFTs. Polycrystalline OTFTs also exhibit pH sensitivity (see Figure 7C,D) according to the manner in which the channel current responds to the ionic strength of the electrolyte solution. To further explore this mechanism, Yan et al. studied OTFTs-based ion-sensitive biosensors in the presence of different cations (Figure 7E,F), showing that the output electrical signal is highly dependent on the amount of cations present in the electrolyte solution. As the concentration of cations increases, the transfer curve shifts to a lower gate voltage. On this basis, acute myocardial ischemia can be monitored using an ion-sensitive OTFT-based biosensor with Ta2O5 as the gate dielectric and P3HT as the semiconductor (Figure 7G). This demonstrates that ion-sensitive OTFTs are applicable to physiological sensing.
4.2 | OTFTs-based glucose biosensors

Glucose level detection is a crucially important parameter for the treatment of patients suffering from diabetes mellitus. For this reason, OTFTs-based glucose biosensors have attracted great attention in the past decades. The detection mechanism uses the Faradaic current induced at the gate electrode via the reaction of glucose and glucose oxidase (GOx). Increased Faradaic currents arise from increased glucose concentration, such that the potential drop decreases at the electrolyte/gate interface and the drain current changes. OTFTs-based glucose biosensors have been developed through immobilizing GOx on the Ta$_2$O$_5$ dielectric layer. Observing changes in the drain current according to the biocatalytic reaction between glucose and GOx, the detection limit of glucose concentration has been characterized to be as low as $10^{-5}$ M. A type of OTFT-based glucose biosensor obtained through the immobilization of GOx on the PEDOT: PSS conducting polymer film is presented in Figure 8A,B. In brief, GOx is entrapped in PEDOT: PSS via electrochemical polymerization, after which the protection of the cellulose acetate membrane is assured by the encapsulation layer. The results exhibit that the drain current...
FIGURE 7  A, Structural diagram of pentacene-based organic thin film transistors (OTFTs). Reproduced with permission from Reference 71. Copyright 2005, AIP Publishing. B, Relationship between $I_{ds}$ and time in the determination of electrolyte solutions with different pH values over 30 minutes. Reproduced with permission from Reference 71. Copyright 2005, AIP Publishing. C, Structural diagram of polycrystalline-based OTFTs with Ag/AgCl as the reference electrodes. Reproduced with permission from Reference 72. Copyright 2011, AIP Publishing. D, Curve of $I_{ds}$ changing with pH values. Reproduced with permission from Reference 72. Copyright 2011, AIP Publishing. E, Structural diagram of OTFTs-based ion-sensitive biosensors. Reproduced with permission from Reference 73. Copyright 2010, American Chemical Society. F, (a) Transfer curves of OTFT in different KCl concentration; (b) illustration of $V_g$ in different cation concentration. G, Enlarged structural diagram of a K$^+$ ion-sensitive OTFTs-based biosensor. Reproduced with permission from Reference 74. Copyright 2008, AIP Publishing
enlarged with the increasing glucose concentration. Results using this system show that drain current increases with increasing glucose concentration. Additionally, another novel OTFT-based enzymatic sensor is shown in Figure 8C;77 this example uses room temperature ionic liquids (RTIL) as a reservoir to enhance the catalytic activity of enzymes. Using glucose/GOx as the reaction model, the detection of glucose concentration from $10^{-7}$ to $10^{-2}$ M has been achieved. This approach has provided a better method for obtaining high-performance OTFTs-based glucose biosensors. To further improve their performance, highly sensitive and selective OTFTs-based glucose biosensors have been obtained as shown in Figure 8D;78 that is, by functionalizing the gate electrodes with GOx, rGO and chitosan/nafion materials. For these biosensors, rGO is used to improve sensitivity and chitosan/nafion materials are utilized to enhance selectivity by increasing the electrode surface to volume ratio at the gate, respectively. As a consequence, an excellent linear concentration dependence curve ranging from 10 nM to 1 mM has been obtained, and a detection limit down to 10 nM has been achieved; this is superior to that of devices without rGO modification and chitosan/nafion materials by approximately two orders of magnitude.

4.3 OTFTs-based DNA biosensors

The application of OTFTs to nucleic acid detection is of great importance for gene expression, bacterial identification, and clinical disease diagnosis. To achieve excellent OTFTs-based DNA biosensors, DNA molecules are used as sensitive probes by immobilization in the OSC layer and electrodes, thereby developing label-free, low-cost OTFTs-based biosensors via facile surface modification. This modification is simply explained as the immobilization of single-stranded DNA (ssDNA) and the formation...
of double-stranded DNA (dsDNA) after hybridization. For example, the fabrication of a DNA-sensitive OTFT-based biological device is shown in Figure 9A, demonstrating that ssDNA molecules can be directly immobilized on the surface of a pentacene film. Furthermore, a novel DNA biosensor based on P3HT polymer is also proposed in Figure 9B, in which ssDNA and dsDNA are differentiated using gold electrodes. These results indicate the promising nature of this technique for sensing DNA hybridization without labeling; however, direct DNA immobilization on the OSC backbone can lead to a decrease in the performance of a device. To prevent the degradation of OSCs, the abovementioned approaches are only applicable in dry state, which are not suitable for real-time sensing applications. To overcome this limitation, a thin maleic anhydride (MA) polymer has been utilized as a modification layer in the development of highly sensitive and specific DDFTTF-based OTFTs for DNA biosensors as shown in Figure 9C. The MA polymer layer facilitates the
attachment of covalent peptide nucleic acid (PNA) strands; these efficiently anchored PNA strands are then used for selective DNA determination. Nevertheless, the inserted MA polymer layer prevents a direct connection being made between the OSC layer and target DNA molecules, limiting the sensitivity of OTFTs-based DNA biosensors. To improve sensitivity, AuNPs are deposited onto the OSC layer with the objective of immobilizing DNA molecules, as depicted in Figure 9D.10 This causes minimal decrease in the performance of OTFTs but increases the sensing ability of OTFTs-based sensors. With the exception of the OTFTs-based sensors mentioned above, a highly sensitive and selective OTFTs-based DNA biosensor is also proposed in Figure 9E.81 Consequently, negatively charged DNA molecules result in variations of the output current.

4.4 | OTFTs-based protein biosensors

As stated previously, biorecognition, such as antibody-antigen recognition, is a central event in the early diagnosis of pathological states and has widespread health-related applications. Several methods, such as enzyme-linked immunosorbent assay, electrochemical biosensors, optical biosensors, and photoelectric biosensors have been applied to antibody-antigen recognition in recent years. Unfortunately, obtaining results from most of these methods requires long timescales and laborious labeling processes. Furthermore, such methods are reliant on expensive instrumentation and lengthy experimental procedures, complicating early diagnosis in patients. OTFTs-based protein biosensors have emerged as an organic diagnosis platform with valuable merits, such as label-free application, low-cost, facile fabrication, and rapid detection relative to traditional immunoassay methods. It has been demonstrated that the modification on gate electrode or OSC layer efficiently improves the sensitivity of OTFTs-based protein biosensors. In terms of modifying the gate electrode, the most common method is Au-S covalent bonding. For example, highly sensitive OTFTs-based histidine-rich protein biosensors have been achieved with NiI11-nta-functionalized gate electrodes as shown in Figure 10A.55 NiI11-nta is able to recognize histidine-rich proteins, and changes in the drain current are observed following the addition of bovine serum albumin (BSA) protein on the gate electrode. Additionally, selective and sensitive chiral recognition biosensors based on OTFTs have been prepared in Figure 10B82 with molecularly imprinted polymer (MIP)-modified gate electrodes. Through modification with different polymeric ion-selective membranes on the gate electrode in Figure 10C,83 selective responses toward K+ and Ca2+ ions have been achieved. Based on changes of the membrane potential at the interface of the gate electrode/electrolyte solution, the ionic signal is transduced to an electrical signal. From the point of view in optimizing OSC modification, Khan et al.84,85 fabricated a label-free pentacene-based OTFT biosensor for selective anti-BSA determination (Figure 10D) through covalent attachment of BSA as a sensitive probe on modified pentacene surfaces. Subsequently sensitive and specific OTFTs-based biosensors have been developed to quantitatively assess the biomolecular recognition of the inflammatory cytokine TNFα as shown in Figure 10E.86 Through protein G modification, more binding sites specific to target TNFα biomolecules are exposed, which greatly enhanced the sensitivity of biosensors. Furthermore, utilizing aptamers, rather than antibodies, as sensitive probes mitigates the charge-screening effect by reducing the length of receptors. OTFTs-based thrombin protein biosensors are shown in Figure 10F.87 Through the decoration of AuNPs binding sites for receptor immobilization on these OSC layers, the detection limit of thrombin protein has reached 100 rM. This result provides an important guideline for tailoring OTFTs to suit their desired biodetection applications.

4.5 | OTFTs-based cell biosensors

Real-time monitoring of cells is critical for studying human health. Bioelectronic devices based on OTFTs are effective as flexible, low-cost, facial, biocompatible, and environmentally friendly approaches. It is therefore desired to develop cell biosensors based on OTFTs for in vivo and in vitro cell monitoring. In Figure 11A,88 an OTFT-based cell biosensor with PEDOT: PSS as the active layer is shown as a tool for monitoring cellular activities in vitro. Because this device is sensitive to changes in surface charges and cell morphology, its mechanism is attributed to electrostatic interactions between the cell and the active layer of the device. Results of using this device demonstrate that the highly electrochemical modulation of conductive polymer films has a significant impact on the behavior of anchoring cells, such as adhesion, differentiation, and proliferation. Figure 11B,89 show that, compared with the single-gate structure, dual-gate organic transistors exhibit better sensing performance toward human mesenchymal stem cells. Using a dual-gate structure improves the ability to tune the optimal sensing bias and expands the material selection toward which OTFTs-based cell biosensors may be directed. Furthermore, real-time monitoring of cell health is a good monitoring indicator for medical applications. Figure 11C90 depicts a biosensor based on OTFTs
conducting real-time toxic effect monitoring of silver nanoparticles (AgNPs) together with the growth of human cells. Cells are initially seeded directly onto the OSCs layer, after which they are used to form a physical barrier capable of regulating ion fluxes. Toxic AgNPs exhibit strong effects on ion fluxes through the cell layer, while nontoxic-treated AgNPs exhibit no significant effects on ion fluxes. Such an approach thus provides a low-cost system for evaluating the toxicity of nanomaterials in vitro, and helps to further clarify the
FIGURE 11  A, Structural diagram of an organic thin film transistor (OTFT)-based cell biosensor with polythiophene doped polystyrene sulfonate (PEDOT: PSS) as the active layer. Reproduced with permission from Reference 88. Copyright 2010, John Wiley and Sons. B, Structural diagram of the solid-liquid dual-gate OTFT device (left), and the $I_{ds}$ changes with time (right) in the detachment and detection of human mesenchymal stem cells. Reproduced with permission from Reference 89. Copyright 2017, American Chemical Society. C, (a) Cross-sectional view of OTFTs-based on PEDOT: PSS. The enlarged view shows cells growing on a PEDOT: PSS film (within the dashed and dotted line); (b) ion flow modified by cytotoxic nanoparticles; (c) ion flow modified by nontoxic nanoparticles. Reproduced with permission from Reference 90. Copyright 2019, John Wiley and Sons. D, (a) Structural diagram of human airway epithelial Calu-3 cells grown on OTFT arrays; (b) structural diagram of OTFTs-based on PEDOT: PSS with tight junctions between cells. Reproduced with permission from Reference 91. Copyright 2013, John Wiley and Sons
nature of interactions between nanomaterials and cells. In addition, miniaturized organic bioelectronic devices are universal platforms that can be functionalized as sensors to monitor and stimulate biological activities at the cell and tissue level via electrical coupling with ion currents. A combination of human airway epithelial cells and the OTFTs array enable the direct coupling of physiological ion currents in the cell with the electrical channel current of OTFT, as reported in Figure 11D.91 OTFT devices may then be used as an electrical output platform to monitor the excitation and inhibition of transported epithelial ions. Mechanisms to sense coupling in such devices largely depend on the sensitive nature of cations. Having a simple electrical output and configuration structure, these devices have great potential for use in studying other physiological activities or as a biosensing platform to evaluate various cell diseases.

4.6 OTFTs-based multianalyte biosensors

Due to its small sample volume requirements and high throughput, OTFTs-based biosensors have great advantages in microanalysis and sensing system. The integration of OTFT arrays and surface-oriented microfluidic systems is shown in Figure 12A.92 The development of OTFTs arrays is of pioneering significance for simultaneous multianalyte detection. As shown in Figure 12, OTFTs are prepared with the patterned PEDOT: PSS channel, three Pt electrodes, and a microfluidic system, guaranteeing multitarget component analysis and enabling analyte solutions to be distributed without the application of external pressure. In addition, since point-of-care detection is a rapidly developing field in biomedical diagnosis, it is urgent to fabricate low-cost and time-effective multichannel devices for next-generation biosensors. A composite OTFT-based platform integrated with a portable “finger-driven” microfluidic system is reported in Figure 12B,93 which not only selectively analyzes specific metabolites, such as glucose, lactate and cholesterol, but also minimizes background interference. These results demonstrate that other types of sensors may be integrated into the array in order to achieve composite and noninvasive point-of-care diagnosis. Moreover, as shown in Figure 12C,94 highly sensitive OTFTs-based sensors may be used to detect glucose and lactic acid. Glucose oxidase or lactate oxidase, together with platinum nanoparticles (PtNPs), are modified on the gate electrode. PtNPs are the key factors required to catalyze and improve the sensitivity of OTFTs-based sensors. The portable sensor has excellent detection performance for real-time and noninvasive determination of glucose and lactic acid concentrations, with detection limits down to $10^{-7}$ and $10^{-6}$ M, respectively. More importantly, early diagnosis and treatment are very important for cancer patients; therefore, it is of great importance to develop innovative technologies suitable for early cancer diagnosis. For example, as shown in Figure 12D,E, Cheng et al.3 prepared a multianalyte biosensor for the simultaneous selective analysis of cytokeratin fragment 21-1 (CYFRA21-1) and neuron specific enolase for lung cancer diagnosis, which is a step toward the development of multianalyte biosensor arrays. Accordingly, a biosensor array was prepared, as shown in Figure 12F,95 for the detection of two kinds of cancer biomarkers, namely CYFRA 21-1 for lung cancer diagnosis and AFP for liver cancer diagnosis. This proposed sensor enables label-free quantitative detection of multianalyte biomarkers. Compared with single-analyte biosensors, this multitarget bio-sensor has good selectivity and appropriate sensitivity, and will be useful for differential cancer diagnosis using simple and rapid detection steps, smaller analytical times, and low sample volume requirements.

5 PROSPECTS AND CONCLUSIONS

The OTFTs-based biosensors integrate the advantages of OTFT devices and biosensors, and therefore attract considerable research attention. Nonetheless, how to achieve reliable and portable OTFTs-based biosensors is a new trend for future developments. The strategies below have been identified as crucial for further development of OTFTs-based biosensors. Appropriate molecular design96-98 and molecular doping99 are required to improve the charge transport characteristics as well as widen the scope of potential sensing applications. Besides, nanoparticle-based probes100 can also create a bridge for the immobilization of biological receptors through bioconjugation chemistry. Furthermore, interface modification36 significantly affect the electrical characteristics as well as improve the performance of OTFTs. Moreover, the optimization of smart materials101-103 and new techniques will improve the fabrication process of reliable and portable OTFTs-based biosensors.

In this mini review, we have summarized recent efforts toward fabricating and functionalizing high-performance OTFTs for numerous biological sensing applications. Biosensors based on OFETs, OECTs, and EGOFETs have been introduced and discussed in detail in terms of the functionalization strategies required to meet specific healthcare and diagnosis applications, such as the detection of ion, glucose, DNA, protein, cells, etc. Novel multianalyte biosensors further enhance the inherent advantages of organic electronics and biological systems.
based on excellent functionalization and operation principles. In this regard, future OTFTs-based biosensors are expected to be more flexible and biocompatible, and should be designed to have stability in water in order to meet the critical requirements of real-time detection in complex biological environments.

**FIGURE 12**  
A. Photograph of a drop of water spread in the microfluidic system on the chip. Reproduced with permission from Reference 92. Copyright 2009, Royal Society of Chemistry.  
B. Structural diagram of an organic thin film transistor (OTFT) array for the selective detection of multiple analytes in complex media. 1) activation “button”, 2) liquid reservoir, and 3) punched inlet. Reproduced with permission from Reference 93. Copyright 2016, John Wiley and Sons.  
C. Structural diagram of OTFTs-based lactate and glucose sensors with microfluidic channels. Reproduced with permission from Reference 94. Copyright 2016, John Wiley and Sons.  
D. (a) Photographs of biosensor chips (10 × 10 mm); (b) configuration of biosensors for the selective detection of multiple cancer biomarkers.  
E. Graph showing the relationship between gate voltage and target protein concentration. The multianalyte detection biosensor is used to selectively detect cytokeratin fragment 21-1 (CYFRA21-1) and neuron specific enolase (NSE) in phosphate buffer solution (PBS) buffer solution. The red bar graph represents the device modified with CYFRA21-1 antibodies, while the blue bar graph represents the device modified with NSE antibodies.  
F. Structural diagram of biosensors for selective multianalyte detection: (a) Device modified with different antibodies for the selective detection of different biomarkers; (b) device A and device B assembled on a chip; (c) immobilization of different antibodies (antibody A, red; antibody B, blue); (d) detection of multitarget analytes in 40 μL buffer solution.
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