REVIEW ARTICLE

Point-of-care biochemical assays using electrochemical technologies: approaches, applications, and opportunities

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Abstract

Against the backdrop of hidden symptoms of diseases and limited medical resources of their investigation, in vitro diagnosis has become a popular mode of real-time healthcare monitoring. Electrochemical biosensors have considerable potential for use in wearable products since they can consistently monitor the physiological information of the patient. This review classifies and briefly compares commonly available electrochemical biosensors and the techniques of detection used. Following this, the authors focus on recent studies and applications of various types of sensors based on a variety of methods to detect common compounds and cancer biomarkers in humans. The primary gaps in research are discussed and strategies for improvement are proposed along the dimensions of hardware and software. The work here provides new guidelines for advanced research on and a wider scope of applications of electrochemical biosensors to in vitro diagnosis.

Introduction

The field of in vitro diagnosis (IVD) has grown rapidly in recent years based on developments in a variety of fields [1]. IVD is the use of specifically designed instruments to detect biological samples collected from humans, including blood, sweat, urine, and tears, to identify diseases [2]. It has attracted significant interest due to its convenience and ability to collect important information [3]. Following the development of the Internet of Things, point-of-care testing (POCT) has come to the fore in the relevant research due to its advantages of portability and wearability in testing procedures. In particular, in the context of the ongoing coronavirus pandemic, inexpensive and rapid response-oriented

diagnostic devices can reduce the cost of medical care [4]. Electrochemical biosensors are applied in POCT owing to their easy portability, simple operation, and reliable performance [5]. Various electrochemical biosensors when combined with different methods have shown significant potential for application to IVD [6]. Many diseases exhibit few specific symptoms in their early phases, because of which patients can easily ignore them such that the appropriate time for treatment passes by. However, many molecules in the body can reflect the health of the patient, including some simple compounds (e.g., glucose and dopamine) and tumor cells. Developing sophisticated and dependable electrochemical sensors for biomarker is thus important for the early detection of such diseases.

Electrochemical sensors are devices that extract and analyze information from reaction signals based on the electrochemical properties of the measured analyte, with the ultimate goal of obtaining information such as concentration. As shown in Fig. 1a, an electrochemical biosensor consists of three main components: a biometric element (e.g., enzyme), a signal converter, and a data analysis module [7]. Its principle of operation is generally based on the use of biometric elements to sense the analyte, and enable physical or chemical reactions through diffusion. The response is then converted by the signal converter into a visually measurable electrical signal that is correlated with the concentration of

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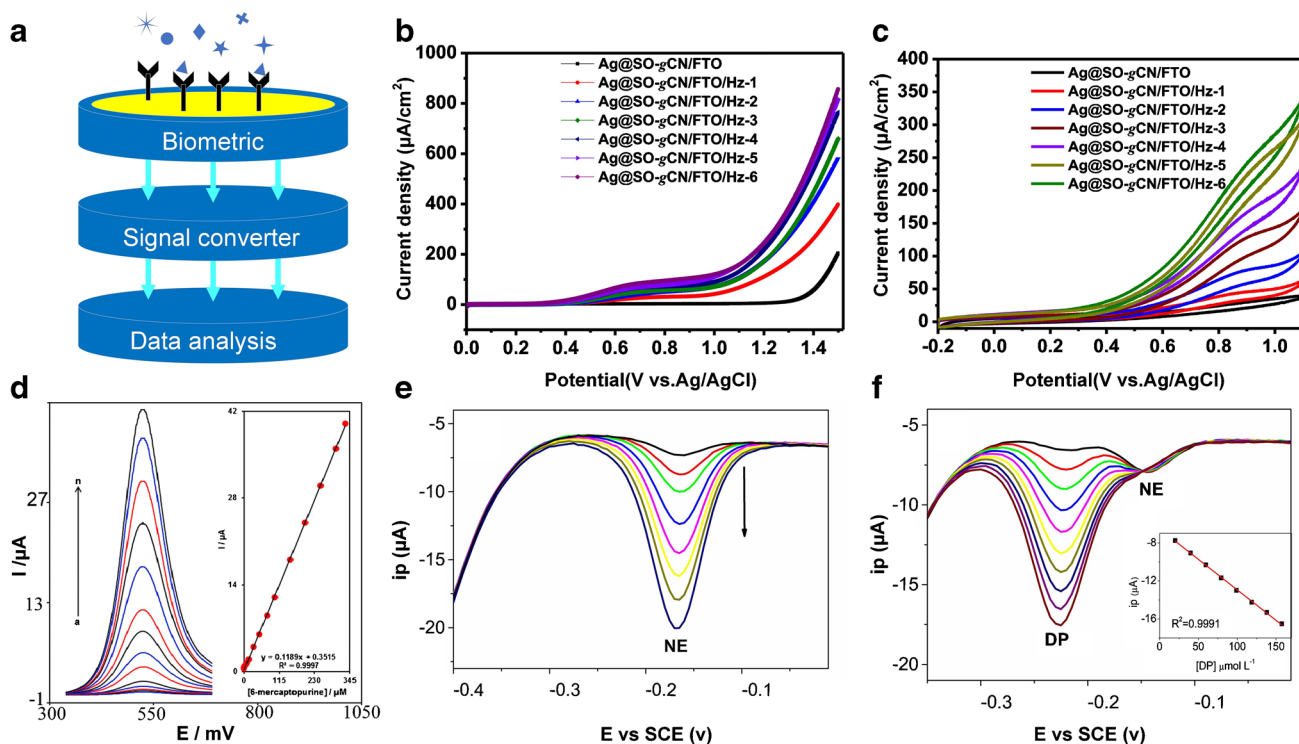
Fig. 1 Voltammetry (LSV, CV, DPV, and SWV) in electrochemical biosensors. **a** The components and principle of electrochemical sensors. **b** LSV responses of Ag@SO-gCN/FTO at varying scan rates (0.02–0.08 V/s) [12]. **c** CV responses of Ag@SO-gCN/FTO at varying scan rates (0.01–0.1 V/s) [12]. **d** DPVs of Fe_3O_4@ppy-Pt/SPE in 0.1 M PBS with a pH of 7, and consisting of distinct concentrations of 6-mercaptopurine [13]. **e** SWV of SiTi/AuNP/CPE with sequential additions of norepinephrine [14]. **f** SWV of SiTi/AuNP/CPE with sequential additions of dopamine in the presence of 1 µmol of norepinephrine [14]

the analyte. The final result is obtained by the data analysis module [8]. Electrochemical biosensors can be categorized according to the process of recognition [9]. Typical devices of this type include biosensors for detecting electrochemical enzyme, immunosensors, and DNA sensors [10].

Duo et al. [6] presented some methods for the detection of biologically important compounds and tumor biomarkers based on the advantages of electrochemical sensing technologies, and briefly summarized the characteristics and applications of these methods. However, detailed analysis and comparison of the various methods as well as the various types of sensors are missing. Sohrabi et al. [11] briefly described the recent progress in cancer biomarker detection based on the direction of portability and pointed out the problems such as tedious sensor preparation process and the need to improve detection performance. Nevertheless, strategies for solving related problems and the prospects for their development have been more generally analyzed. Therefore, it is essential to consider the mechanisms of the equipment, to identify the problems step by step, and to offer solutions.

This review highlights the applications of and recent advances in electrochemical biosensors in the context of IVD, where the aim of these devices is to monitor the physiological health of the patient for the early detection of markers of diseases. We fully consider and compare four well-known methods of electrochemical detection. Following this, the development of three common electrochemical biosensors and their associated applications are examined. Then the limitations as well as their principles of operation are detailed. Typical applications of sensors that operate according to different principles are then summarized in conjunction with the corresponding methods of electrochemical detection in the field of IVD. Finally, outstanding challenges in the area and prospects for further advances in electrochemical biosensors are sketched out.

Major methods of electrochemical detection

Various methods of electrochemical detection have been proposed to verify the preparation of electrochemical sensors and quantitatively analyze the analytes. Four methods of detection frequently used to this end: voltammetry, electrochemical impedance spectroscopy, chronoamperometry, and electrochemiluminescence. The results obtained by these methods are closely related to the type and concentration of the analyte, thus allowing for corresponding qualitative and quantitative analyses.

Voltammetry

Voltammetry is the most commonly used method in electrochemical testing, and involves investigating how the electrode current fluctuates with the applied potential during an electrochemical reaction. Voltammetry may be classified into linear-sweep voltammetry (LSV), cyclic voltammetry (CV), differential-pulse voltammetry (DPV), and square-wave voltammetry (SWV) according to different modes of potential control.

LSV involves applying a linearly varying potential between the working and the counter electrodes with a linear fit to the peak current for qualitative and quantitative analyses. However, this method is normally carried out for only qualitative analysis as it is susceptible to a wide range of factors. The main difference between CV and LSV is that the potential control in the former is "low–high" One-way linear input, while the latter is a "low–high–low" voltage cycle. The reversibility of the electrochemical reaction can thus be determined by the symmetry between the curves. To improve the sensitivity of detection based on voltammetry, DPV involves controlling the modes of input of the potential by replacing the original linear input with a pulsed form. The input of SWV consists of two pulses in opposite directions compared to DPV. In summary, all the above four methods can be used for quantitative analysis based on the output current or the difference in current.

Each of the four types of measurement described above has different effects in various cases. The appropriate measurement solutions should be chosen to meet the specific diagnostic needs. Hydrazine is a well-known carcinogen that can cause adverse health effects, such as respiratory problems, liver and kidney problems, and skin corrosion. Akbar et al. prepared Ag@SO-gCN/FTO-based electrochemical sensors by using well-crystallized silver nanoparticles, and used both LSV and CV for the detection of hydrazine [12]. They found that the sensitivity and limit of detection of LSV were 2.01 $\mu A \cdot mM^{-1} \cdot cm^{-2}$ and 0.164 ± 0.013 μM, respectively, whereas those of CV were 2.305 $\mu A \cdot mM^{-1} \cdot cm^{-2}$ and 0.143 ± 0.011 μM, respectively (results are shown in Fig. 1b and c). This shows a sensor that combines these two electrochemical methods can be used to monitor the concentration of hydrazine with high sensitivity and low detection limit. Somayeh et al. fabricated an Fe_3O_4@ppy-Pt/SPE electrochemical sensor, and combined CV, LSV, and DPV to assess the use of 6-mercaptopurine, a chemotherapeutic agent for the treatment of inflammatory bowel disease [13]. The results of CV confirmed that the nanomaterials considered can increase electrochemical activity while LSV verified the increase in the rate of electron transfer. DPV was used to fit the linear relationship between the peak response current and the concentration of the analyte to be measured (Fig. 1d).

The detection limit has been greatly improved compared to the former, down to 10 nM.

Glycopyrrolate is an anticholinergic drug with strong inhibition of gastric juice secretion and mild gastrointestinal antispasmodic effects. Muneer et al. [15] used three methods, CV, DPV, and LSV, to study the electrochemical activity of the drug. The results of cyclic voltammetry tests showed that the redox reaction of glycopyrrolate on surface of the working electrode was reversible. LSV and DPV were used for the estimation of concentration of the drug, and yielded sharper peaks. The experimental results revealed that peaks of the response current for each concentration were remarkably different and could be clearly distinguished. The two methods of detection were then analyzed and compared. On the one hand, the curve of calibration of LSV had a higher correlation coefficient (0.9990 vs. 0.9860) and a lower detection limit (0.016 mg/mL vs. 0.025 mg/mL) than that of DPV. On the other hand, the authors also investigated the effects of the additives in commercially available glycopyrrolate in terms of recoveries and relative standard deviations, which represent the accuracy and precision of each method, respectively. The results showed that the relative standard deviation of the LSV method was much smaller than that of the DPV method while its recovery was also lower than that of the DPV method. Therefore, each method has its advantages.

SWV can deliver excellent results owing to its low detection limit and sensitivity to detection. In particular, it has the potential to achieve simultaneous monitoring of multiple targets. Franciele et al. use specially designed SiTi/AuNP/CPE electrodes for the detection of two important neurotransmitters, norepinephrine (NE) and dopamine (DP) [14]. Figure 1e shows the results of detection of NE by using SWV in the range of concentration of 20–180 μM, with significant peaks in the current for each concentration profile. After fitting the values of current to the concentrations, the sensitivities of the detection of NE and DP were 0.096 μA μM^{-1} and 0.074 μA μM^{-1}, respectively, with limits of detection of 0.26 μM and 0.34 μM, respectively. These properties are superior to other electrochemical sensors. Interestingly, the peak currents for both NE and DP differed by 100 mV in the direction of voltage, which increased the likelihood of monitoring the concentrations of both substances simultaneously. Figure 1f shows curves of SWV at concentrations of 20 to 180 mM of DP in the presence of 1 μmol of NE. It is clear that the peaks of detection of the two substances did not interfere with each other and could be clearly distinguished.

Electrochemical impedance spectroscopy

The principle of electrochemical impedance spectroscopy (EIS), which regards an electrochemical system as a black-box model, is to feed the system with a perturbation signal

and analyze its electrochemical properties by observing the corresponding response signal. It differs from voltammetry in that the disturbing electrical signal input to the EIS is neither direct voltage nor current, but an alternating potential wave with a small amplitude and varying frequency, which ultimately measures the impedance. It is also possible to record the changes in the phase angle at a frequency corresponding to the impedance [6].

EIS allows for the electrochemical system to be analyzed in a variety of ways, starting with the electrochemical characterization of the electrodes. This makes it possible to determine whether the electrodes have been successfully prepared. Caffeic acid is widely used in food, medicine, and nutraceuticals for its ability to prevent heart disease and reduce inflammation and mutations [16]. Aijuan et al. proposed a CuZnO$_x$/MWCNT composite electrode for the detection of caffeic acid, and its effectiveness was directly related to the detection-related performance of the entire sensing system [17]. The feasibility of the electrodes was assessed by using EIS and other methods of electrochemical detection, where EIS helped determine the characteristics of the electrodes, and to obtain information on electron transfer between the electrolyte and the surface of the electrode. Figure 2a shows the electrical impedance

spectra of MWCNT, CuZnO$_x$, and CuZnO$_x$/MWCNT in 0.1 M KCl containing 5 mM Fe(CN)$_6^{3-/4-}$, with the insets illustrating the equivalent circuit. Rs, Rct, and Zw indicated the resistance of the electrolyte, resistance to charge transfer, and the Warburg impedance, respectively. The Rct value of the CuZnO$_x$/MWCNTs-modified electrode was 4.21 Ω, significantly lower than those of the other two modified electrodes (6.83 Ω and 5.35 Ω). This indicates that CuZnO$_x$/MWCNT has good electron transfer capability. These results verified the synergistic effect of both CuZnO$_x$ and MWCNT, and confirmed the successful preparation of the electrode such that it delivered excellent electrochemical performance.

EIS can also serve as a tool for the quantitative analysis of the analytes. Toxic heavy metals in water are an important contributor to human health [18]. Hiba et al. used a natural ion carrier, lignin, to modify the Pt electrode for the detection of Pb^{2+} ions, and analyzed the output response of the constructed electrochemical sensor using EIS [19]. Figure 2b shows the Nyquist curves for different concentrations of Pb^{2+} ions (10^{-9}–10^{-4} M) in the range of frequency of 100 mHz–100 kHz, using which the curves of calibration of the impedance values and concentrations of the Pb^{2+} ion at a fixed excitation frequency (1 Hz) were plotted. The limit
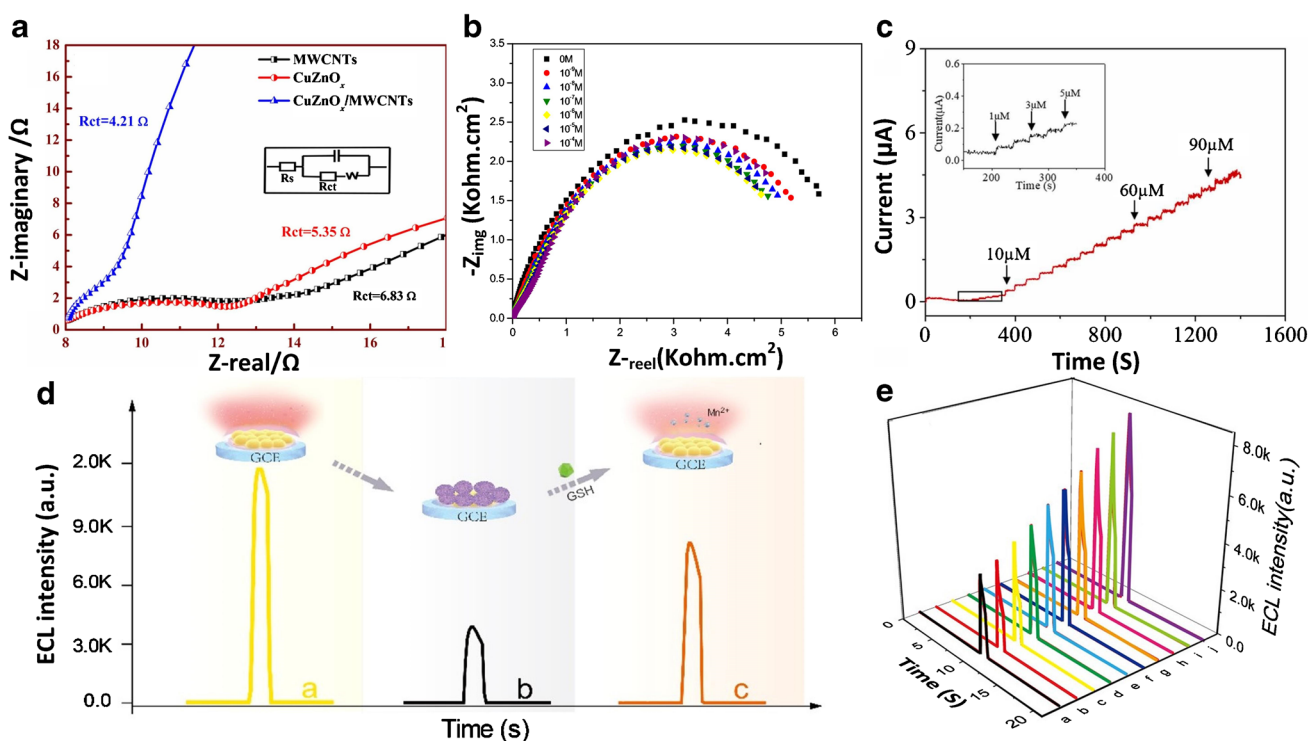

Fig. 2 Methods of electrochemical detection in biosensors. **a** Nyquist plot of MWCNTs, CuZnO$_x$, CuZnO$_x$/MWCNTs (inset), and their equivalent circuit [17]. **b** Nyquist plots for the detection of different concentrations of Pb.$^{2+}$ in 1 M KNO$_3$ [19]. **c** I–t curves of ZnO/ Ti$_3$C$_2$T$_x$/Nafion-modified gold electrode with different concentrations of DA [22]. **d** ECL–time curves of the MnO$_2$/AuNC-based sensing platform for the detection of ATP [28]. **e** ECL response of the split-type ECL sensor for different concentrations of ATP [28]

of detection of the manufactured sensor was $10^{-9.5}$ M, lower than those reported in other studies [20, 21].

Chronoamperometry

Chronoamperometry functions by recording the curve of variations in the current of the electrochemical sensor after feeding a single-step potential or double-step potential to the electrochemical system. As the electrochemical reaction occurs, the current tends to rise first but then decreases and reaches a certain peak over time as the quantity of the analyte decreases. Each peak current signal is used to quantitatively analyze the test object. In early research in the area, chronoamperometry was implemented to estimate the concentrations of certain compounds. Jingyu et al. created a composite electrode by using a metal–organic framework material (ZIF-8) in combination with tyrosinase to quantitatively analyze levodopa through chronoamperometry [22]. As shown in Fig. 2c, different concentrations of dopamine as analyte were added several times, and the curve of variations in the current of the electrode was recorded. A significant and abrupt change in the magnitude of current corresponding to the addition of each sample was observed. Depending on the fitting results of the peak currents, the low detection limit and wide linear range could be obtained. More importantly, the sensor coupled with a wireless electronic circuit (Bluetooth) allowed for convenient monitoring by using a smartphone.

The chronoamperometry method can also be used to test the repeatability and stability of electrochemical sensors. Jinchun et al. fabricated H_2O_2 electrochemical sensors based on molybdenum dioxide–gold–silver nanoparticle composites [23]. The response of the sensor was analyzed using chronoamperometry, and the curve of variations in the response current was recorded for successive additions of 1 mM H_2O_2 to five electrodes under the same conditions. The relative standard deviation of the electrodes was 3.79%. The authors also performed electrochemical measurements on the same electrode at 4-h intervals. The curves of the response current did not completely overlap, but the calculated relative standard deviation was negligibly small at 3.09%. These results show that the electrochemical sensor had outstanding repeatability and stability.

Electrochemiluminescene

Electrochemiluminescence is a combination of the electrochemical method and the chemiluminescence method. The principal mechanism involves generating specific substances through electrochemical methods and then using them to combine or react with other materials to produce luminescence. It has the advantages of electrochemical methods including high sensitivity, wide linear range, and simple

instrumentation, and chemiluminescence methods including stable reagents, easy control, and good reproducibility. Thus, it offers promise for use in immunoassay, nucleic acid hybridization analysis, and the detection of various compounds [24]. Peipei et al. developed a PTC-DEPA/KCC-1 NCS-based sandwich electrochemiluminescent immunosensor to identify calcitoninogen (a bacterial infection biomarker) [25]. Both DEPA and KCC-1 enhanced the intensity of luminescence of the luminol PTCA (perylene-3,4,9,10-tetracarboxylic acid). This strategy made use of the sensitivity of the immunosensor, and the detection of $S_2O_8^{2-}$ in the solution led to two peaks of intensity (double signal) with a lower detection limit of 0.017 pg·mL^{-1} than in past studies [26, 27]. Furthermore, the appropriate selection of materials with unique capabilities may contribute to improving the detection-related performance of the devices. Zhongnan et al. [28] developed an ultra-sensitive MnO_2/AuNC-based sensing platform for the detection of adenosine triphosphate (ATP) based on the principle of electrochemiluminescence (Fig. 2d). Figure 2e illustrates ECL signals corresponding to 10 concentrations of ATP. An ultra-low detection limit of 1.4 fM was obtained. The detection limit has been significantly reduced compared to previous studies (32 nM).

In conclusion, methods of electrochemical detection can be classified into voltammetry, EIS, chronoamperometry, and ECL based on differences in the detected signals. All these methods can be used for the quantitative analysis of the target. In the context of voltammetry, CV can also distinguish between the reversibility of electrochemical reactions. DPV can be used for the detection of trace substances owing to its low background current and high detection sensitivity. EIS can identify the effects of modifications in the electrode by monitoring the changes in impedance because it acquires the impedance spectrum of the sensor over a wide range of frequencies to provide more information on electrode dynamics and the structure of the interface than other methods. Chronoamperometry is a process in which a step voltage is fed and the electrode current is recorded as a function of time. In this process, the target can be added at certain intervals so that the electrical signals corresponding to different concentrations of the target are available. Chronoamperometry is thus faster than other methods. Electrochemiluminescence combines the chemiluminescence method, which uses the intensity of luminescence of the luminol to determine the quantity of the analyte. Electrochemiluminescence has the characteristics of high selectivity and sensitivity but also has the disadvantage of being susceptible to environmental influences. All of these methods can be used for detection and evaluation in electrochemical experiments. The final choice of technique can be made in accordance with the results of the response of each method. It is also possible to combine as many methods as needed to achieve the best detection-related performance.

Categories of electrochemical biosensors

Electrochemical enzyme biosensors

The enzyme is the sensitive element of an enzyme biosensor, which has evolved in three main stages [29]. The first generation of enzyme biosensors was based on oxygen-mediated catalytic reactions, and indirectly quantified the analytes by measuring the oxygen consumed by the reactions or the substances produced (e.g., hydrogen peroxide). Sensors developed based on this principle were first reported in 1962, when Leland et al. proposed a glucose enzyme sensor combined with an oxygen electrode for monitoring oxygen consumption [30]. The results of such sensors are susceptible to the influence of oxygen in the background environment, resulting in poor resistance to interference. To overcome this drawback, an electron mediator is used as the electron acceptor instead of oxygen. It can circulate electrons between the redox center of the enzyme and the working electrode to generate oxidation current, which is measured to determine glucose concentration. However, the second-generation enzyme biosensor may still be affected by oxygen in the environment due to competition between the electron mediator and oxygen, and may encounter problems with toxicity due to mediator leakage. Further improvements are thus still

needed [31]. Third-generation enzyme biosensors enable direct electron transfer between the enzyme and the working electrode by introducing novel nanomaterials modified for the surface of the electrode. This can facilitate the immobilization of the enzyme on the surface of the electrode to directly facilitate the transfer of electrons without environmental interference. Recent research on the principle of third-generation enzyme biosensors has led to the development of sensors that have delivered good performance [32, 33]. Meng et al. prepared the corresponding sensors by immobilizing glucose oxidase and lactate oxidase on screen-printed carbon electrodes (Fig. 3a) for the quantitative analysis of glucose and lactate concentrations in human sweat, respectively [34].

Electrochemical immunosensors

Electrochemical immunosensors combine methods of electrochemical analysis with immunological techniques. A specific antigen or antibody is often immobilized on the surface of the sensor, and specifically binds to analytes containing the corresponding antibody or antigen to ensure the detection of the analyte (concentration) [35]. Because of the strong binding force between antigens, antibodies, and other biomolecules, the immunosensor possesses excellent selectivity and is highly sensitive. Electrochemical immunosensors are extensively used.
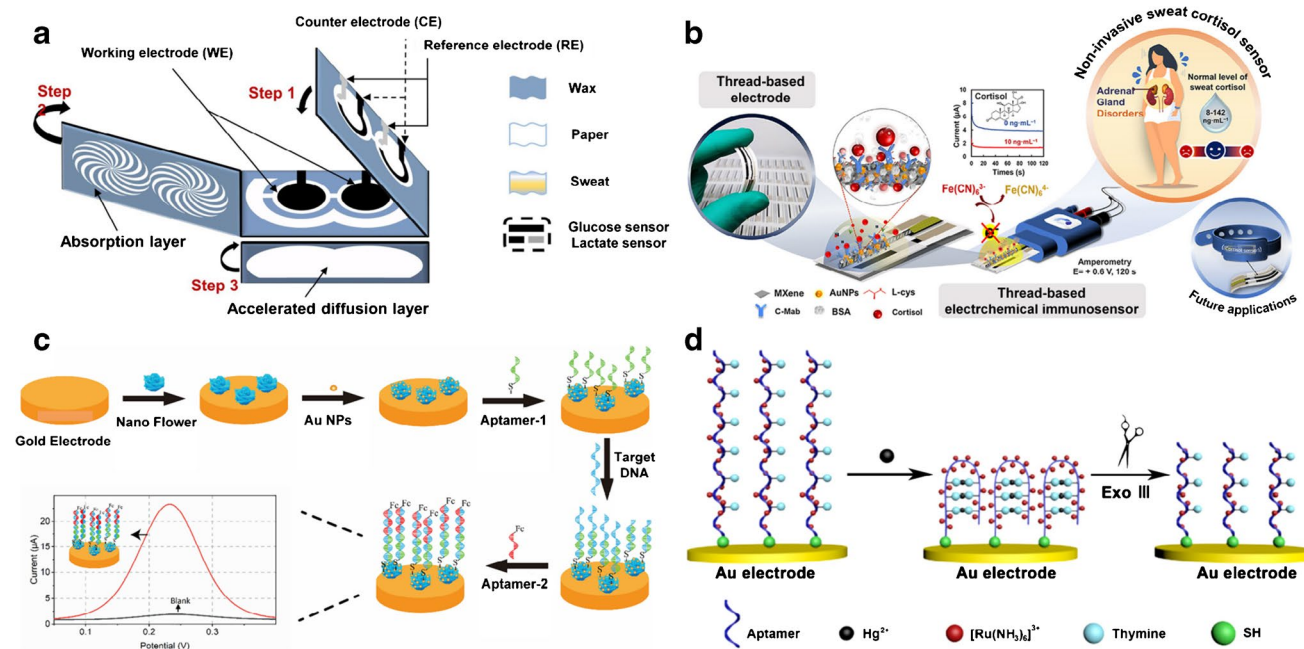

Fig. 3 Applications of different types of electrochemical biosensors. **a** Structural anatomy of highly integrated sensing paper for the detection of glucose and lactate [34]. **b** Non-invasive electrochemical immunosensor for detecting cortisol in sweat. [36]. **c** Schematic representation of the stepwise fabrication of the E-DNA sensor [41]. **d** Illustration of the sensing principle of electrochemical Hg.$^{2+}$ DNA sensor [42]

Thidarut et al. developed a thread electrochemical immunosensor through the fixation of anticortisol and the modification of specific functional materials for the detection of cortisol [36]. The MXene and AuNPs that were prepared to enhance the immobilization of specific antibodies, because of which the sensor had a low detection limit of 0.54 ng mL^{-1} as well as good specificity and stability (Fig. 3b). The sensor was assembled into a thread structure to allow for wearable monitoring. Electrochemical immunosensors are also widely used in other fields. Fabiana et al. have summarized the potential for their use in applications of food and environment analysis as well as cancer biomarker diagnosis [37]. They also discussed the physical and chemical methods used for their preparation.

Electrochemical DNA biosensors

Owing to the outstanding biocompatibility and capability of biomolecule recognition of the DNA, electrochemical DNA biosensors have shown distinct advantages in terms of detection in various applications. These sensors first immobilize the DNA as a recognition probe on the surface of the electrode of the sensor and use it to capture specific biomolecules. The response of the captured biomolecules is then converted into a measurable electrical signal, which enables the detection of the analyte. The DNA is an organic substance with a complex molecular structure in the body that can be considered a marker for many infectious diseases, notably the chronic hepatitis B viral (HBV) infection. HBV infection is a disease of the human metabolic system that affects nearly 2 billion people globally [38]. On the one hand, the traditional method for detecting HBV is to use an enzyme-linked immunosorbent assay (ELISA) to identify the state of infection, but this method focuses mainly on the relevant antigens or antibodies, and does not represent the critical phase of viral replication [39]. On the other hand, the polymerase chain reaction (PCR) can be used to measure this stage, but this has the disadvantages of being complex, time consuming, and costly [40]. Hence, simple, highly sensitive, and stable biosensors need to be developed. Electrochemical DNA biosensors have exhibited these properties in recent years. Feijun et al. used novel nanoparticles, gold nanoparticles, and two surface-immobilized aptamers to exploit a highly selective electrochemical DNA biosensor that could detect the concentration of the DNA to detect HBV over a linear range [41]. It yielded low detection limits of 1.10×10^3–1.21×10^3 copies/mL and 1100 copies/mL (Fig. 3c). Other than their use for diagnosing infectious diseases, electrochemical DNA sensors may also be suitable for food safety and ecological monitoring. Hg^{2+} is a typical, toxic, heavy metal ion that can endanger the environment and the health of people. Xuan et al. developed an electrochemical DNA sensor based on thymidine–Hg^{2+}–thymidine that was experimentally confirmed to be able to identify Hg^{2+} in samples of river water over a wide linear range of 1 pm–1 μM (Fig. 3d) [42].

In conclusion, each type of sensor varies due to its principle, and the appropriate one should be applied and optimized depending on practical needs. Electrochemical enzyme sensors have the advantages of high sensitivity and excellent selectivity, whereas the activity of the enzyme is still susceptible to external interference. Integrating a temperature sensor or a pH sensor into the system should be considered to correct for bias. Moreover, the immobilization of enzymes is a challenge for device fabrication. Even though many nanomaterials have been developed to facilitate immobilization, improvements in them are required. Enzyme-free sensors provide novel avenues for better performance design. Owing to the strong specific binding capability between the antigen and the antibody, electrochemical immunosensors exhibit higher selectivity and sensitivity than other biosensors. The immobilization of biomolecules (antibodies or antigens) and the amplification of electrical signals generated by electrochemical reactions are two important factors affecting the performance of immunosensors. A number of materials, including a noble metal nanomaterial and carbon-based materials, have been used to enhance the immobilization of biomolecules and amplify the signals [43]. However, some couples (e.g., AgNP-biomolecules) can affect the sensitivity and stability of the sensor due to aggregation such that their capacity for amplification is limited. Therefore, it is necessary to explore more reliable materials or other strategies to develop satisfactory sensing devices [44]. Electrochemical DNA sensors, which use DNA probes as the sensitive unit, have the advantages of a quick response time and simple operation. However, it is also important to pay attention to the way in which DNA molecules are immobilized. Nanomaterials with excellent conductivity and rate of electron transfer need to be explored to enhance molecular immobilization. The density and orientation of DNA probes are important factors affecting the sensitivity and stability of DNA biosensors, and can be designed to form novel polyhedral structures to improve the detection-related performance of the sensors (e.g., TSP). In addition, the above sensors have problems with the compatibility of the biological samples and practical wearability, and require the incorporation of additional disciplinary technologies to yield more accurate and stable real-time monitoring devices.

Biological application of electrochemical biosensors

Advances have recently been reported in IVD with the rise of noble technologies in electrochemistry. Nanotechnology-based IVDs are widely available for disease diagnosis, and are highly sensitive, specific, and convenient [45]. Traditional medical devices are generally large-scale instruments,

while IVDs are gaining increasing attention from researchers due to their convenience, rapidity in the diagnosis of biological samples. In a nutshell, patients who receive information about health abnormalities benefit from timely treatment. Electrochemical biosensors are electrochemical instruments that act as signal converters. They convert the concentration of the analyte to a measurable electrical signal to allow for the real-time monitoring of biomarker-related information. Electrochemical biosensors have the advantages of easy miniaturization, high sensitivity, stability, and low cost, and thus have a wide range of applications in many areas. In medical diagnostics, many biological compounds that are markers of diseases, such as glucose, uric acid, cholesterol, and dopamine, can be detected using them. Electrochemical biosensors have also played an important role in the detection of tumor markers.

Electrochemical biosensors for the detection of biological compounds

Glucose is an important criterion in the clinical diagnosis of diabetes and is associated with complications such as stroke, blindness, and heart disease. The traditional method of drawing blood to obtain information on glucose concentrations often causes pain or discomfort, and even poses the risk of infection, whereas other body fluids, such as the saliva, sweat, tears, and urine, offer advantages in terms of their non-invasive availability [46]. Depending on the electrode material used, they can be divided into enzyme sensors and non-enzyme sensors [47]. Kavyashree et al. [48] combined silicon carbide nanoparticles (SiCNPs) and electrospun nanofiber membranes (ENFM) with a structure that facilitated the immobilization of glucose oxidase, and produced an electrode with a sensitivity of 30.75 µA mM^{-1} cm^{-2} for glucose detection (Fig. 4a). The outputs of measurements using the chronoamperometry method are shown in Fig. 4b. However, the difficulty of immobilizing enzymes, and the susceptibility of enzyme activity to temperature and the pH limits their application, whereas non-enzymatic sensors have the advantage of excellent stability and high sensitivity. Therefore, metal oxides and nanocomposites are the preferred methods to improve their detection-related performance. Mei et al. [49] fabricated a non-enzymatic glucose sensor based on Co$_3$O$_4$ nanoparticles that exhibited high sensitivity and selectivity in detecting glucose levels in the human serum and saliva. As shown in Fig. 4c, the response of the prepared electrodes was
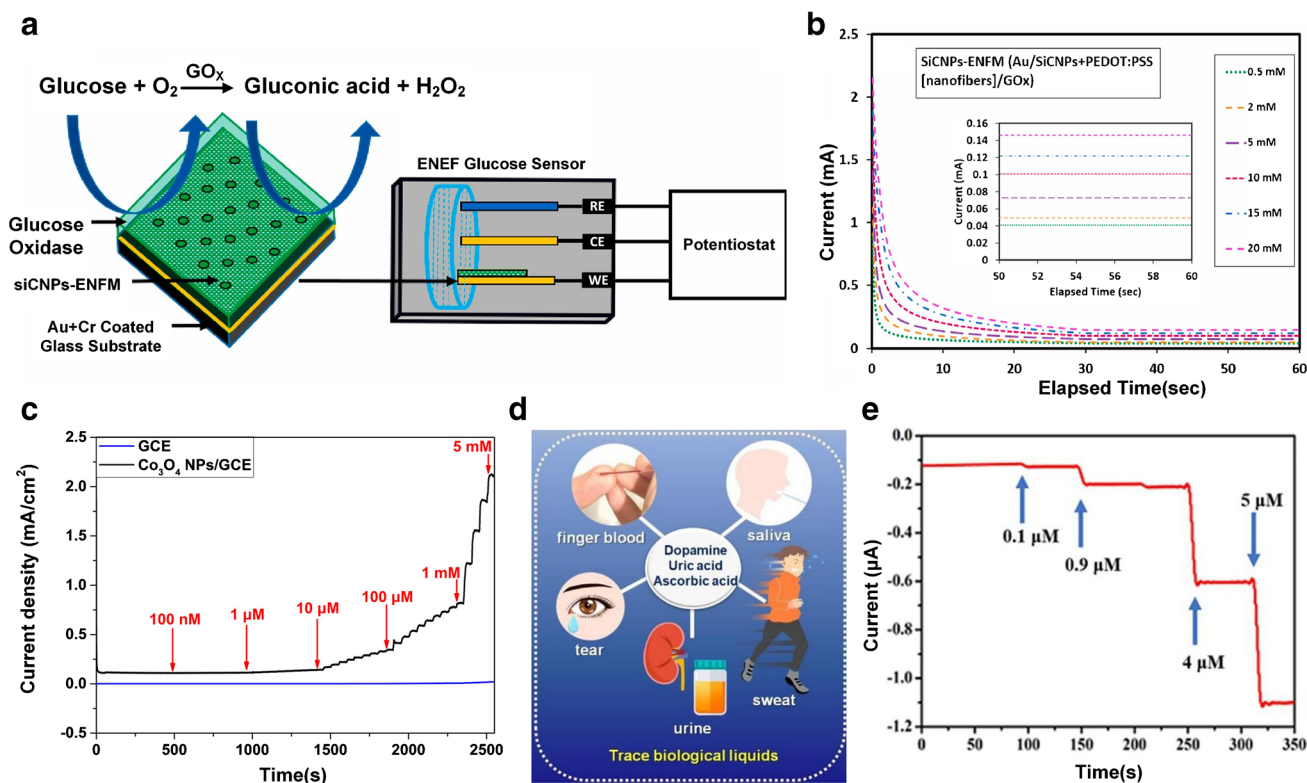

Fig. 4 Electrochemical biosensors for the detection of biological compounds. **a** Pictorial representation of the SiCNP–ENFM glucose-sensing electrode [48]. **b** Chronoamperometric graphs of SiCNP–ENFM Au/SiCNP–PEDOT:PSS (nanofibers)/GOx electrodes at a potential of +0.6 V [48]. (**c**) Amperometric responses of the as-prepared Co$_3$O$_4$ NPs/GCE to glucose oxidation [49]. **d** The detection of DA in IVDs [51]. **e** I–t curves of ZnO/Ti$_3$C$_2$T$_x$/Nafion-modified gold electrode with different concentrations of DA (0.1–1200 µM) [54]

much higher than that of the bare electrode GCE, regardless of the presence of the glucose to be measured. Figure 4c and its inset depict the curve of variations in the response of the electrode current with the addition of glucose and the corresponding fitted curve, respectively. As the concentration gradually increased, the current increasingly quickly. The sensitivity of the sensor to glucose detection was 2495.79 $\mu A \cdot mM^{-1} \cdot cm^{-2}$, with a correlation coefficient R^2 of 0.99575 and an ultra-low detection limit of 9.3 nM. Sensors prepared for glucose in recent research and their relevant properties are summarized in Table 1. Specifically, it is important to identify indicators such as the sugar content of foods to ensure the health of diabetics. Some studies have exclusively used foods such as milk as the object [50].

Dopamine (DA) is of great interest to a number of investigators because of its key physiological role in the regular working of the nervous system. Microfluidic devices and nanotechnology provide the possibility of monitoring biomolecules, such as DA, in trace volumes of such fluids as sweat, tears, and saliva through in vitro monitoring (Fig. 4d) [51]. Many methods are available for the detection of DA, such as fluorescence spectroscopy [52] and surface-enhanced Raman spectroscopy [53]. However, electrochemical methods have the advantages of simplicity, high speed, high sensitivity, and low cost over them. Mingchao et al. [54] fabricated a $ZnO/Ti_3C_2T_x/Nafion/Au$ composite electrode by using $Ti_3C_2T_x$, a two-dimensional material with large specific surface area and excellent properties. The ZnO nanostructure had an important influence on catalytic activity and enables the effective determination of the target dopamine. Figure 4e and its inset show the curve of the response of the electrode and the corresponding fitted curve of the peak current–dopamine concentration for each stage of the addition of dopamine as recorded by chronoamperometry, respectively. The results showed that the electrode had an ultra-wide linear range of detection (0.1–1200 μM) and a low detection limit (0.076 μM). The sensors prepared to identify DA in recent research and their relevant properties are summarized in Table 1.

Other biological compounds in the human body are also critical to health, and also require wearable electrochemical sensors so that they can be quickly and accurately tracked. Uric acid (UA) is closely related to cardiovascular and renal diseases as well as being an important indicator of gout. Many studies have examined monitoring it based on sweat, and this has the potential to reduce the risk of gout in clinical medicine [55, 56]. Cholesterol levels are also important for human health. When excess cholesterol is present in the body, it can lead to hypercholesterolemia or worse, atherosclerosis, and chronic inflammation. A number of systems have been developed to regularly monitor cholesterol in the body [57]. The electrochemical biosensors used for UA and cholesterol detection are summarized in Table 1.

Electrochemical biosensors for the detection of tumor markers

Cancer has long been a major global public health problem. Malignant tumors are the origin of cancer, and certain substances are produced and released in the cells or body of the host in the form of antigens and enzymes. Therefore, substances that are quantitatively or qualitatively altered in the patient's body fluids or tissues are often used as tumor markers for the early screening and timely treatment of cancer. Typical tumor markers include prostate-specific antigens (PSAs), circulating tumor cells (CTCs), and alpha-fetoprotein (AFP). Electrochemical sensors have been widely explored because of their advantages of low cost, portability, and robustness against interference.

Prostate cancer is among the six most common causes of natural death among men, because of which the status of the corresponding tumor requires long-term monitoring and real-time treatment [58]. The concentration of PSA is higher in patients with prostate cancer than in normal persons, and thus it is generally considered an early indicator of the disease [59]. Compared with traditional ELISA methods, electrochemical biosensors eliminate the complex requirements of large instruments and specialized analytical skills, and have the advantages of high sensitivity, rapidity, and low cost [60]. The preparation of electrodes is crucial for the effectiveness of the entire system in the context of electrochemical methods. The activity and large surface area of nanomaterials can improve the rate of electron transfer and even the stability of the sensor. They have thus attracted considerable attention in the domain of electrochemical sensors [61, 62]. Suresh et al. [63] coated fullerene–C_{60}, polyaniline, and palladium nanoparticles in a layer by layer manner onto a glassy carbon electrode through the drop-in and electrodeposition methods. The first antibody Ab1 was then immobilized. More drops of the PSA to be detected and bound to Ab1 were incubated. Finally, Ab2-HRP was immobilized. CV was used to quantify the latter by recording the peak current and the corresponding PSA concentration for H_2O_2 reduction (Fig. 5a). The authors applied the prepared sensor to samples of serum and urine to demonstrate its feasibility and reliability. It had a range of linear detection of 1.6×10^{-4} $ng \cdot mL^{-1}$ to 38 $ng \cdot mL^{-1}$ and a low limit of detection of 1.95×10^{-5} $ng \cdot mL^{-1}$. The detection limit and linear range of the prepared sensors further improved when materials with special structures and properties were used. Quan et al. [64] use the porous network structure of the complex MoS_2 GAs (molybdenum disulfide graphene nanomaterials) to provide a large specific surface area for gold nanomaterials, and the final composite had good electrical conductivity for the preparation of electrochemical immunobiosensors with a wide linear range and low detection limit (Fig. 5b). Changes in response signals for different concentrations of

Table 1 The electrochemical biosensors for the detection of biological compounds

| Analyte	Detection technique	Electrode	Linear range	Sensitivity	Limit of detection	Real sample	Ref
Glucose	DPV	Pd-doped ZnO NRs/GCE	-	$0.64\ \mu A\ \mu M^{-1}\ cm^{-2}$	$0.3\ \mu M$	Serum	[81]
	Chrono-amperometry	Ag-PANI/rGO	0.1–$50\ \mu M$	$2.7664\ \mu A\ \mu M^{-1}\ cm^{-2}$	$0.79\ \mu M$	Organic liquids (milk, orange juice, cola)	[50]
	Chrono-amperometry	Cu NPs-LIG	$1\ \mu M$–$6.0\ mM$	$495\ \mu A\ mM^{-1}\ cm^{-2}$	$0.39\ \mu M$	-	[82]
	DPV/EIS/CV	FcBA/glucose/3APBA/4MBA/AuNPs/ITO	0.5–$30\ mM$	$0.56\ \mu A\ mM^{-1}\ cm^{-2}$	$43\ \mu M$	Urine	[83]
	Chrono-amperometry	LSG/PBSE/PtNPs/Gox/nafion	0.0025–$2.5\ mM$	$12.64\ \mu A\ mM^{-1}\ cm^{-2}$	$2.35\ \mu M$	-	[84]
	Chrono-amperometry	Co3O4 NPs/GCE	0.01–$0.1\ mM$ 0.1–$3\ mM$	$2495.79\ \mu A\ mM^{-1}\ cm^{-2}$ $408.89\ \mu A\ mM^{-1}\ cm^{-2}$	$9.3\ \mu M$	Saliva	[49]
	Chrono-amperometry	Au/SiCNPs-PEDOT:PSS-PVDF-ENFM/GOx	0.5–$20\ mM$	$30.75\ \mu A\ mM^{-1}\ cm^{-2}$	$0.56\ \mu M$	-	[48]
	Chrono-amperometry	GOx/PtNPs/rGO/Au	0.2–$1\ mM$	$29.10\ \mu A\ mM^{-1}\ cm^{-2}$	$200\ \mu M$	Sweat	[85]
	Chrono-amperometry/DPV	MB/Ti$_3$C$_2$T$_x$/SPCE	0.08–$1.25\ mM$	$2.4\ nA\ \mu M^{-1}$	$17.05\ \mu M$	Sweat	[34]
Dopamine	CV	Au NPs/N-doped CN$_{900}$	0.02–$700\ \mu M$	$0.60\ \mu A\ \mu M^{-1}\ cm^{-2}$	$7\ nM$	Serum	[86]
	DPV	Ti-C-T$_x$/GCE	0.5–$50\ \mu M$	-	$0.06\ \mu M$	Urine	[87]
	Chrono-amperometry	ZnO/Ti$_3$C$_2$T$_x$/Nafion/Au	0.1–$1200\ \mu M$	-	$76\ nM$	Serum	[54]
	Chrono-amperometry	ED-CuSe	$50\ pM$–$20\ \mu M$ 40–$320\ \mu M$	$0.64\ \mu A\ mM^{-1}\ cm^{-2}$	$26.80\ \mu M$	Urine	[88]
		HT-CuSe	0.050–$20\ \mu M$ 40–$640\ \mu M$	$2.7664\ mA\ mM^{-1}\ cm^{-2}$	$8.80\ \mu M$		
	DPV	GQDs-MWCNTs	0.005–$100.0\ \mu M$	-	$0.87\ nM$	Serum	[89]
	CV	NC/MWCNT	1–$200\ \mu M$	-	$80\ nM$	Sweat, serum	[90]
	CV/chrono-amperometry	CuO-MgO	10–$100\ \mu M$	$69\ \mu A\ mM^{-1}\ cm^{-2}$	$6.4\ \mu M$	Sweat	[91]
	Chrono-amperometry	PEDOT-G-TYR	5–$70\ \mu M$	$12.9\ nA\ \mu M^{-1}\ cm^{-2}$	$101\ nM$	Tear	[92]
	DPV	Mn-MoS2/PGS	0.05–$500\ \mu M$	-	$50\ nM$	Sweat	[93]
	DPV	NB-GF@ Co–N-CNTAs	$10\ nM$–$10\ \mu M$	$2.17\ mA\ mM^{-1}\ cm^{-2}$	$10\ nM$	Sweat, tear, saliva, urine	[51]
Urine acid	Chrono-amperometry	PEDOT:PSS hydrogel/CPE	2.0–$250\ \mu M$	$0.875\ \mu A\ \mu M^{-1}\ cm^{-2}$	$1.2\ \mu M$	Sweat	[55]
	SWV	CB-PLA	1–$70\ \mu M$	-	$0.28\ \mu M$	Sweat	[94]
	DPV	Co3O4–ERGO/SPE	5–$500\ \mu M$	$46.5\ nA\ \mu M^{-1}\ cm^{-2}$	$1.5\ \mu M$	Saliva	[95]
	Chrono-amperometry	Uricase/MWCNTs/SPE	5–$1000\ \mu M$	-	$0.33\ \mu M$	Saliva	[96]
	DPV	PEDOT-GO/ITO	2–$1000\ \mu M$	-	$0.75\ \mu M$	Saliva	[97]
Cholesterol	CV	Bienzyme nanoparticle	5–$675\ mg/dL$	-	$0.18\ mg/dL$	-	[57]
	DPV	Chit/ChOx/Ti$_3$C$_2$T$_x$/GCE	0.3–$4.5\ nM$	$132.66\ \mu A\ nM^{-1}\ cm^{-2}$	$0.11\ nM$	Serum	[98]
	LSV/DPV	Pencil lead electrodes	0.625–$9.375\ mM$	$1455.22\ \mu A\ mM^{-1}\ cm^{-2}$ (LSV) $323.38\ \mu A\ mM^{-1}\ cm^{-2}$ (DPV)	-	Serum	[99]
	Chrono-amperometry	Pt-NC/enzyme/Nafion	2–$486\ \mu M$	$132\ \mu A\ mM^{-1}\ cm^{-2}$	$2\ \mu M$	Saliva	[100]
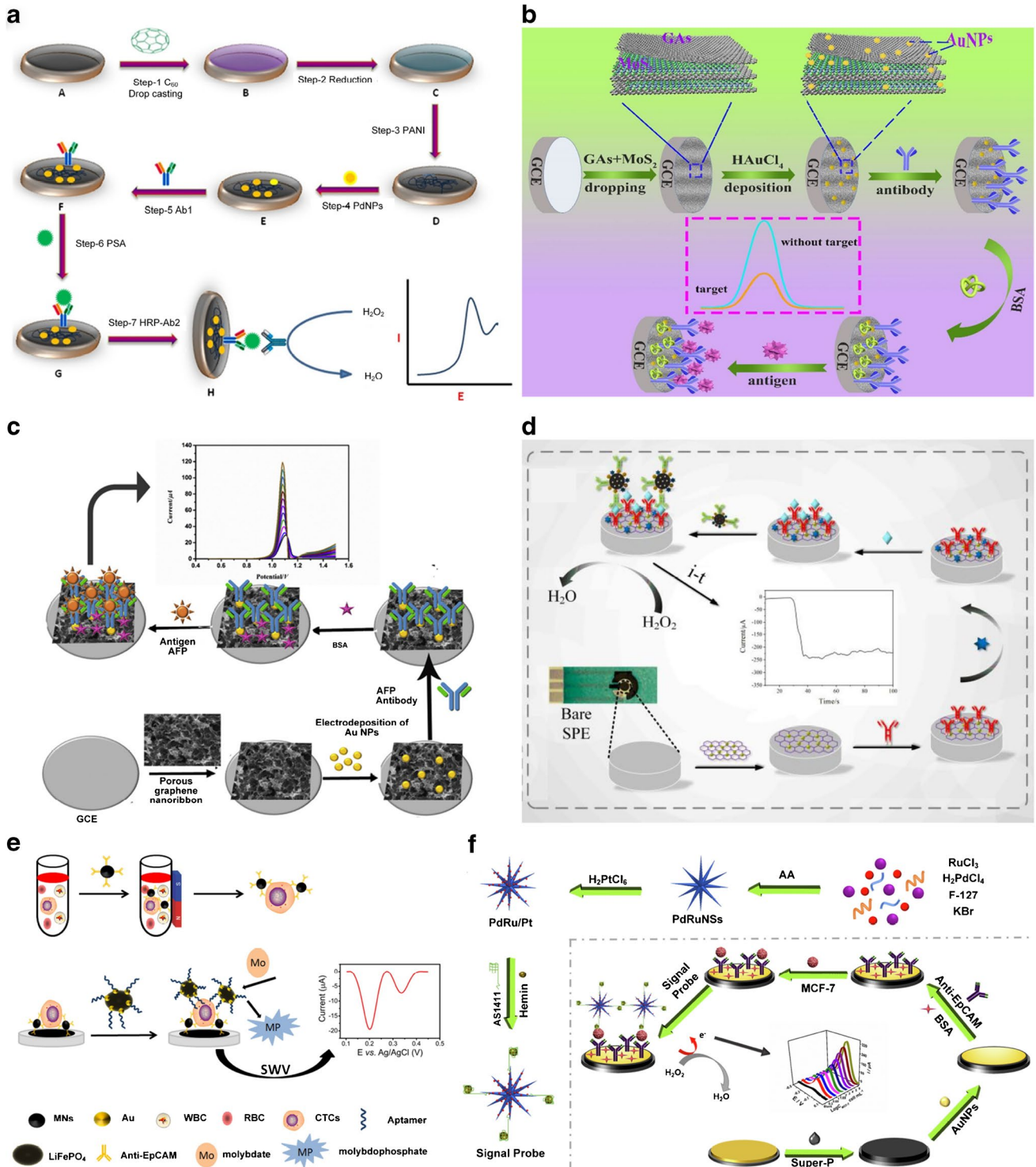
Fig. 5 Electrochemical biosensors for the detection of tumor markers. **a** Illustration of procedure for the fabrication of an immunosensor for detecting PSA [63]. **b** The fabrication and detection of an immunosensor for PSA [64]. **c** Schematic representation of the AuNPs/PGNR/GCE electrochemical immunosensor for the detection of AFP [66]. **d** Schematic illustration of the electrochemical biosensor for detecting AFP [67]. **e** Schematic representation for the detection of circulating tumor cells [69]. **f** Schematic representation for the detection of circulating tumor cells [70]

Table 2 The electrochemical biosensors for the detection of PSA and AFP

Analyte	Detection technique	Electrode	Linear range	Sensitivity	Limit of detection	Real sample	Ref
PSA	Chrono-amperometry	$Ti_3C_2T_x$-$NiWO_4$	1.2×10^{-6}–1.8×105 ng mL^{-1}	/	150 fg mL^{-1}	Saliva	[101]
	CV	HQ@CuNPs-reduced-fullerene-C_{60}/GCE	0.005–20 ng mL^{-1}	/	2.0 pg mL^{-1}	Serum, urine	[102]
	CV	PdNP@PANI-C_{60}/GCE	0.00016–38 ng mL^{-1}	-	19.5 fg mL^{-1}	Serum, urine	[63]
AFP	SWV	Thi-Au-Fe3O4@ZIF-8	1.0×10^{-5}–50 ng mL^{-1}	-	3 fgmL^{-1}	Serum	[103]
	DPV	AuNPs/PGNR	5–60 ng mL^{-1}	-	1 ngmL^{-1}	Serum	[66]
	CV	anti-AFP/Cu_2O/MWCNTs-Au/GCE	0.001–40 ng mL^{-1}	-	0.3 pgmL^{-1}	Serum	[104]
	DPV	HCS@PANI	0.001–80 ng mL^{-1}	-	0.3 pgmL^{-1}	Serum	[105]
	EIS	Label-free DMIP	$10-10^4$ pg mL^{-1}	-	3.3 pgmL^{-1}	Serum	[106]
	SWV	BSA/AFP-Apt/PtNPs/GO-COOH/SPGE	3–30 ng mL^{-1}	-	1.22 ngmL^{-1}	Serum	[107]
	DPV	AuPt-VG(vertical graphene)/GCE	1 fg mL^{-1}–100 ng mL^{-1}	43.3 µA (lg (pg mL^{-1}))$^{-1}$	0.7 fg mL^{-1}	Serum	[108]
	Chrono-amperometry	MoS2@Cu2O-Au	0.1 pg mL^{-1}–50 ng mL^{-1}	-	37 fg mL^{-1}	-	[109]

the PSA were finally recorded by differential pulse voltammetry. The linear range and detection limit of the sensor were derived from the calibration curve.

Hepatocellular carcinoma is disease that causes a large number of deaths. It is characterized by a marked increase in alpha-fetoprotein (AFP) as a typical biomarker during stages of the disease [65]. Monitoring AFP is thus necessary for the early diagnosis of hepatocellular carcinoma. Strategies such as enzyme-labeled amplification have been developed to improve the sensitivity of the assay, but their application has been limited by the susceptibility of the enzyme activity to environmental influences. Alternatives are thus needed. Composite nanomaterials can combine the properties of single materials. Lavanya et al. [66] exploited the excellent mechanical properties of graphene nanoribbons to prepare an AFP/AuNPs/PGNR/GCE electrochemical immunosensor based on gold nanoparticles as support material. The linear range and detection limit of the sensor were 5–60 ng/mL and 1 ng/mL, respectively, by the DPV method (Fig. 5c). The immunosensor developed by Haolin et al. [67], using this strategy, based on special nanomaterials has a higher sensitivity (Fig. 5d). On the one hand, the modification of graphene with thioine and tetraethylene pentamine not only retains the large specific surface area and good electrical conductivity of the original, but also improves its biocompatibility. On the other hand, a mesoporous material, ordered mesoporous carbon, has been used as a signal probe to facilitate signal amplification, and has the characteristics of high porosity and excellent adsorption. The response curves of the sensor to different concentrations of AFP were recorded by the chronocurrent method as well as a calibration curve of the peak current and the corresponding concentration. The linear range and limit of detection were thus greatly improved to 0.005–100 ng·mL^{-1} and 0.0022 ng·mL^{-1}, respectively.

Electrochemical biosensors have also enabled the direct detection of tumor cells. CTCs distribute in the peripheral blood system, leading to the spread of toxic substances and the progression of disease [68]. The rapid detection and effective control of CTCs are important. Wenzuo et al. [69] used epithelial cell adhesion molecule (EpCAM)-modified Fe_3O_4 magnetic nanoparticles to capture CTCs and gold nanoparticles-modified $LiFePO_4$ as a detection probe (Fig. 5e). Electrochemical signals from the reaction of phosphate with molybdate were recorded by means of SWV. The linear range and LOD of the sensor were 3–10,000 cell·mL^{-1} and 1 cell·mL^{-1}, respectively. In addition to integrating various materials, Xi et al. [70] designed structures to facilitate signal amplification and fabricated electrochemical biosensors with hemin/G4 DNAzyme-PdRu/Pt heterostructures (Fig. 5f). The former also introduced small particles of conductive carbon black to improve the sensitivity of the assay, while the latter exhibited high catalytic activity. The results of differential-pulse voltammetry showed that the linear range of detection was significantly extended to 2–106 cells mL^{-1}, with a lower limit of detection of 2 cells mL^{-1}. The electrochemical biosensors used to detect tumor markers are summarized in Table 2.

The human body has various indicators of its health. The implementation of non-invasive IVD devices is emerging as a desirable option for the real-time monitoring of these substances. Prevalent investigations have encompassed the detection of universal biological compounds and tumor cells. Recent research on the in vitro detection of certain typical biomarkers is summarized in Table 1. Devices for the detection of simple and common compounds, such as glucose, have been extensively researched and developed. Their detection-related performance has been gradually improved with the use

of new nanomaterials and techniques. Moreover, indicators (e.g., PSA) of cancer can now be detected using samples of urine and saliva. Tumor cells that induce worsening cancer can also be identified by electrochemical biosensors. However, although many electrochemical biosensors for in vitro detection have been developed, both their sensitivity of detection and stability should be further investigated. Other markers that may have a higher correlation with cancer can also be explored in samples of biological fluids to assist in screening for the disease. Furthermore, even though many of the developed biosensors have yielded good results in the laboratory, more efforts should be invested in testing them in clinical trials. Only then can we be certain of their feasibility and reliability.

Conclusions, challenges, and perspectives

This review systematically discussed and compared the basic principles of various electrochemical biosensors and the working effects of various detection methods. As summarized in this review, electrochemical biosensors based on different principles and combined with a variety of approaches for detection have been successfully used in IVDs, and have made a remarkable contribution to helping monitor and maintain the health of patients. The performance of each sensor (sensitivity, detection limit, linear range, etc.) has been continuously improved with the incorporation of novel functional materials and the adoption of experimental preparation methods that have been gradually optimized. It is promising that experiments with actual body fluid samples provide support for achieving realistic wearable IVDs. Although these sensors offer promise for use in lab applications, there is a long way to go before their large-scale rapid screening.

The World Health Organization has imposed requirements on the performance-related aspects of wearable devices in terms of stability, immunity to interference, and real-time connectivity [71]. Although research on electrochemical biosensors has widened their linear range, lowered their limit of detection, and improved their sensitivity, there is considerable room for improvement before they can be applied to clinical testing. The performance of the present electrochemical sensors has been significantly improved in terms of sensitivity and detection limit, but there is a need for enhancement in the aspects of interference immunity, stability, continuity, and portability. Achieving successful clinical practice requires multiple considerations. On the one hand, the amount of these analytes in body fluids such as sweat, urine, and tears is much less than in blood. Thus, the detection of these substances requires higher selectivity and sensitivity of the equipment. These requirements are also one of the current technical difficulties. In the past 5 years, the detection and extraction of weak signals have been the core problem that researchers have mainly focused on. Yet, the continuity detection and stability of electrochemical sensors should become one of the central themes of future research. On the

other hand, making devices portable and wearable is the prevailing trend now and in the future. In order to achieve a truly wireless real-time monitoring wearable system, the size of the device should also move towards greater miniaturization. Several mini electrochemical analyzers are already commercially available, but the expensive price would make the cost of the whole instrument significantly higher. In addition, sample collection for IVD may be difficult. Sweat could accumulate on the skin surface due to heat or increased heart rate, but different sweat collection methods would correspond to different results. In order to detect certain substances in sweat, a variety of ways, typified by exercise and iontophoresis-induced method, can be used for the extraction of sweat. However, some studies have found ambiguous correlations between the results of different sampling conditions. Therefore, the appropriate choice of sweat collection method needs to be further investigated.

In order to achieve a deeper and more comprehensive understanding of the process, it is essential to combine experimental research with intelligent data analyses. The current prospects for the development of electrochemical biosensors could be considered in two directions: one path is based on hardware to improve their basic sensing performance and the other approach is based on intelligent software to optimize and improve the functionality of the working system. The immobilization of sensitive materials on electrodes is a key step in the detection performance of sensors. More new nanomaterials and advanced microfabrication techniques should be explored to facilitate the immobilization of functional materials to improve the properties of sensors. Electrochemical enzyme sensors can make use of organic molecules (e.g., polyacrylamide), materials with porous frameworks such as metal organic frameworks and stabilizers to enhance the immobilization of the enzyme [72]. Similar approaches apply to electrochemical immunosensors, electrochemical DNA sensors, and other types of devices as well [73–75]. Furthermore, in order to miniaturize and produce electrochemical biosensors on a large scale, microfluidic techniques could be ingeniously utilized in sweat sampling. A "cut-and-paste" method has been used to pattern and transfer polydimethylsiloxane and polyethylene terephthalate films to efficiently fabricate microfluidic chips [76]. Additionally, in order to reduce the problem of oversized devices resulting from peripheral devices and power supplies, technically small functional modules such as bluetooth and near field communication can effectively be integrated into the system. This contributes to the wearability of the device and ensures that measurement data can be transmitted and stored in real time with great flexibility. It is worth mentioning that machine learning provides a powerful aid to improve the performance for devices. Multilayer perceptrons and convolutional neural networks can classify a large number of samples [77–79]. The YOLO algorithm can improve the ability of sensors to recognize reaction areas [80]. Last but not least, although the data obtained from health monitoring can be displayed and stored for real-time monitoring in combination with intelligent software. However, it

cannot be ignored that there are vulnerabilities such as leakage of private user information and loss of data. Consequently, more algorithms can be further explored and compared, while more precise algorithms may be refined, thus enabling the development of devices that are more flexible for individual design and application. We anticipate that more detailed analysis will be conducted in the near future to resolve these issues satisfactorily.

Declarations

Conflict of interest The authors declare no competing interests.

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