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Recent advance in *in vivo* potentiometry for probing brain chemistry

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Highlights:

- Summarizes recent advances in potentiometric sensors regarding sensing materials, response mechanisms, and detection of various ions and molecules.
- Reviews the applications of potentiometric sensors for *in vivo* sensing and prospects future development in this field.

Abstract: The development of tools for precisely recording neural chemical signals is crucial for understanding the dynamic chemical changes in the brain during physiological and pathological processes. Currently, *in vivo* electroanalysis based on implantable microelectrodes has become an important means for analyzing neural chemical signals in the brain. Among them, potentiometry, as one of the electrochemical methods, plays an important role in life science research due to its advantages such as miniaturized design, portability, low power consumption, and excellent neuronal compatibility. In recent years, the introduction of new sensing materials and the understanding of theoretical potential responses have enabled potentiometric biosensors to detect analytes of interest with high precision and sensitivity, ranging from non-electrochemically active substances such as ions to electrochemically active small molecules and even larger biomolecules. This article reviews the latest research progress of potentiometric sensors in brain sensing, including the response mechanism of potential and their applications in the field of *in vivo* analysis of brain neurochemistry.

Keywords: potentiometry; *in vivo* electroanalysis; ion-selective electrode; galvanic redox potentiometry; neurochemical substance

1. Introduction

The structure and function of the nervous system fundamentally depend on the interactions, conversions, and spatiotemporal distribution dynamics of chemical substances. Therefore, dynamically detecting *in vivo* variations of neurochemical substances is crucial for elucidating the essential mechanisms of complex physiological processes such as cognition and emotional regulation. These chemical substances mainly include neurotransmitters such as dopamine (DA), acetylcholine, glutamate and serotonin (5-HT),

neuromodulators such as ascorbic acid (AA), ions such as H^+, Ca^{2+}, Mg^{2+}, Na^+ and K^+, energy metabolism-related molecules such as glucose and ATP, as well as free radicals such as reactive oxygen species [1–5]. Developing and improving chemical analysis methods applicable to the *in vivo* level to achieve high spatiotemporal resolution dynamic monitoring of these substances is of great significance for clarifying the molecular basis of brain function and the pathogenesis of brain diseases, and will further deepen our understanding of the essence of life activities [6,7]. However, compared with *in vitro* analysis, the complex and dynamic environment within the brain poses significant challenges to *in vivo* analysis of neurochemical substances. Implantable microelectrode electrochemical sensing technology, with its advantages of high spatiotemporal resolution, highly designable sensing interface, and minimal interference with brain tissue, has become an important tool for dynamic monitoring of brain chemistry and has made remarkable progress in this field [8].

At present, electrochemical analysis methods are mainly divided into three categories, including voltammetry, amperometry and potentiometry. The choice of these methods mainly depends on the chemical properties of the analyte and the differences in experimental conditions. By reasonable selection, specific analysis of the target substance can be achieved [5,9]. Among them, voltammetry and amperometry have the advantages of fast response time and the ability to precisely identify based on the different redox potentials of the analyte [5,10,11], and have been widely used in the monitoring of neurochemical substances *in vivo*. As a type of voltammetry, fast-scan cyclic voltammetry (FSCV) enables real-time quantitative measurement of neurotransmitter release with subsecond resolution. Wightman *et al.* [12,13] employed FSCV to simultaneously record instantaneous changes in oxygen and DA levels under electrical stimulation *in vivo*. In contrast to voltammetry, amperometry does not achieve resolving power by scanning potential waveforms. It relies on specially designed electrode surface/interface that enable electrochemical reactions exclusively for target molecules based on their intrinsic redox properties. Hou *et al.* [14] immobilized aptamers on carbon fiber electrode (CFE) surfaces via non-covalent interactions of cholesterol alkyl chains, and combined this strategy with amperometry to realize *in vivo* detection of DA. Vaneev *et al.* [15] implanted platinized nanoelectrodes into single cells to perform real-time amperometric monitoring of reactive oxygen species responses in tumor-bearing mice during chemotherapy.

However, the detection efficiency of these techniques is closely related to the redox properties of the target analyte (including 5-HT, DA, norepinephrine and epinephrine, *etc.*), and their response signals are easily affected by the surface state of the microelectrode [16–18]. It is particularly worth noting that the tissue damage caused by the implantation of the electrode probe *in vivo* and the non-specific adsorption of biomacromolecules on the sensing interface can significantly reduce the electroactive area, thereby affecting the detection sensitivity, signal stability and working life of the amperometric and voltammetric sensors [19]. In addition, traditional electrochemical analysis methods mainly rely on the working principle of the electrolytic cell, and the measurement process requires the application of an external polarization voltage. This characteristic limits their synchronous application with electrophysiological recording techniques [20]. Potentiometry, as one of the electrochemical methods, works based on the potential difference formed between the working electrode and the reference electrode under open-circuit conditions [21]. This method realizes the determination of the target chemical substance by real-time monitoring of this potential change and converting it into a quantifiable electrical signal [22,23]. Compared with other electrochemical detection techniques, potentiometric

analysis has a lower dependence on the surface state of the electrode, and can effectively overcome the interference of non-specific adsorption of biomacromolecules in *in vivo* detection; at the same time, the working electrode is in an open-circuit state during measurement, and the current in the detection circuit is close to zero [19,24]. Based on this characteristic, potentiometry does not cause electrical interference to the electrophysiological activities of the nervous system or other instruments used simultaneously in the *in vivo* detection process [20]. In recent years, potentiometry-based *in vivo in situ* analytical techniques have made significant progress in life sciences and medical research, providing valuable data support for both fundamental research and clinical applications.

In the early days of *in vivo in situ* analysis, potentiometry was mainly applied to the detection of non-electroactive substances such as ions, but it was difficult to effectively analyze molecules with redox properties. The most typical example is the ion-selective electrode (ISE), which accurately measured the activity of target ions by constructing a specific recognition interface [25–28]. The development of ISEs began in the early 20th century when Cremer discovered the phenomenon that the potential of a glass membrane changes with the pH of the solution [29]. In 1961, Pungor first prepared a halide-selective electrode using a heterogeneous membrane, which marked a breakthrough in this field [30,31]. Since then, various key types of ISEs have emerged, including crystal membrane ISEs [32], neutral ionophore-based liquid membrane ISEs [33], and charged ionophore-based liquid membrane ISEs [34]. During this period, plasticized polyvinyl chloride (PVC) gradually became the common matrix for liquid membranes and has been used to this day [35,36]. Subsequently, research on ISEs based on solid and liquid membranes has continued to deepen, and related technologies have entered a stage of rapid development [37,38]. ISEs have been widely applied in fields such as *in vivo* detection due to their ability to perform real-time and continuous detection of complex biological samples without the need for complex pretreatment. The history of using micro-scale ISEs based on polymer membranes for *in vivo* measurements can be traced back to 1959 when Hinke *et al.* first used micro-tube electrodes to measure the ion activity within cells [39]. Since then, this technology has continued to develop. For instance, in 1975, Thomas *et al.* reported a liquid-contact ISE based on a micropipette and successfully measured Li^+ directly within snail neurons [40]. However, despite the wide application of liquid-contact ISEs in *in vivo* and single-cell analysis, their performance is still constrained by the design of the internal filling solution. The main limitations include the susceptibility of the internal filling solution to environmental factors such as temperature and pressure, which reduces the stability and lifespan of the electrode [41,42]. Additionally, the difference in ionic strength between the sample and the internal filling solution can cause osmotic pressure changes, leading to fluctuations in the volume of the internal filling solution. This may cause delamination of the ion-selective membrane (ISM) and reduce detection sensitivity [43]. Moreover, the internal filling solution system is difficult to further miniaturize, which restricts the size reduction of the device [38]. Although nanoscale electrodes have been developed, their high impedance characteristics result in significant noise and slow response, further limiting their practical application and development [44]. Therefore, optimizing the electrode structure design to improve its durability has become a key direction for the development of ISEs. One of the most promising approaches is to introduce an internal solid contact (SC) layer to replace the traditional internal filling solution.

In 1971, Cattrall and Freiser fabricated the first solid-contact ISE (SC-ISEs) without an internal filling solution and named it the “coated wire electrode” (CWE), which is considered the earliest primitive prototype of modern SC-ISEs [45]. This electrode has a simple structure, with a high-molecular

sensing membrane containing a Ca^{2+} ionophore directly coated on the surface of a metal wire, and it shows a good Nernstian response to Ca^{2+}. Subsequently, Freiser *et al.* further extended the CWE to the detection of other ions [46]. Although this electrode has a large potential drift due to the instability of the metal/membrane interface potential, this pioneering work laid the foundation for the development of SC-ISEs [37,42,47]. In 1992, Lewenstam and Ivaska *et al.* proposed introducing polypyrrole (PPy) as an intermediate SC layer between the ion-selective ISM and the conductive substrate to address the aforementioned issues. This layer is also known as the "ion-electron transduction layer" [48]. This structure can convert changes in ion concentration into electronic signals and effectively stabilize the potential at the substrate/ISM interface, becoming the typical design of current SC-ISEs. Since then, researchers have successively developed various transduction layer materials, including conductive polymers, various carbon materials, nanomaterials, and molecular redox couples, significantly enhancing the potential stability of SC-ISEs and promoting their extensive attention in practical applications. The emergence and gradual maturation of solid-contact electrodes are regarded as an important advancement in potentiometric sensing structures [47,49]. By improving the conduction and connection between the sensitive membrane and the conductive substrate, this type of electrode ultimately overcomes the limitations of traditional liquid-filled types and is more conducive to the miniaturization, integration, and flexibility of devices.

In recent years, driven by the introduction of new materials and the development of the sensing mechanism of SC-ISE from the traditional zero-current potentiometry to the multi-readout mode dynamic potentiometry, potentiometry based on ISE has evolved into a key modern analytical technique. Its application scope has also expanded from the detection of simple ions to the determination of proteins, DNA, enzymes, and other bioactive substances [50–54]. Besides the potentiometry based on ISE mentioned above, a series of effective potentiometric detection methods for electroactive neurotransmitters have been established through innovative electrochemical analysis principles. For instance, by establishing a stable chemical equilibrium through reversible electrochemical reactions, the concentration of the target substance can be accurately determined. Zhang *et al.* proposed a principle that utilizes the reversible redox process of Ag^+/Ag_2S and the strong binding ability of Ag^+ with H_2S ($K_{sp} = 6.0 \times 10^{-49}$) to establish a Nernst equilibrium under open-circuit conditions, thereby developing a new electrochemical method to generate a potential output related to the concentration of H_2S [21]. However, this method is only applicable to reversible electrochemical processes. In irreversible systems or complex mixed systems (such as the detection of AA *in vivo*), the thermodynamic equilibrium potential of the analyte is often difficult to achieve on the working electrode. Considering this situation, the Mao research team has innovatively developed a redox potentiometry technology based on the galvanic cell working mechanism (galvanic redox potentiometry, GRP) in recent years [20].

Taken together, benefiting from the introduction of novel materials, the design of multi-functional sensors, and the development of new sensing principles, potential-type sensors have demonstrated significant application value in the study of brain neural chemical processes. However, although significant progress has been made in this field, it is still in the exploratory stage for practical *in vivo* applications and deserves in-depth research and development. This article discusses various potentiometric response mechanisms, then elaborately explores the application of *in vivo* analytical techniques based on these mechanisms in brain neurochemical research, and looks forward to their potential for future development.

2. The basic principles of ISE and its application in *in vivo* analysis

2.1. The basic principles of ISE

Based on the potentiometric method using ISEs, the response exhibits a complex time-dependent characteristic. This response characteristic is determined by the properties of the electroactive material (membrane/film), the composition of the electrolyte, the state of the membrane-solution interface, as well as the chemical composition, thermodynamic and kinetic properties of the entire system. All these characteristics are the research objects of response theory modeling. Currently, the theoretical models for ISE responses mainly include the classical model (Figure 1a) and the diffusion layer model (Figure 1b). The classical model avoids the mathematical and computational difficulties caused by solving nonlinear equations by ignoring the ionic migration effect, and can provide guidance on the basic principles of the response for sensor users. The diffusion layer model, as a more advanced modeling method, can more fully and accurately describe the spatial and temporal variation characteristics of the sensor response. Given that the classical model is easier to understand and express, this article will mainly focus on discussing this model.

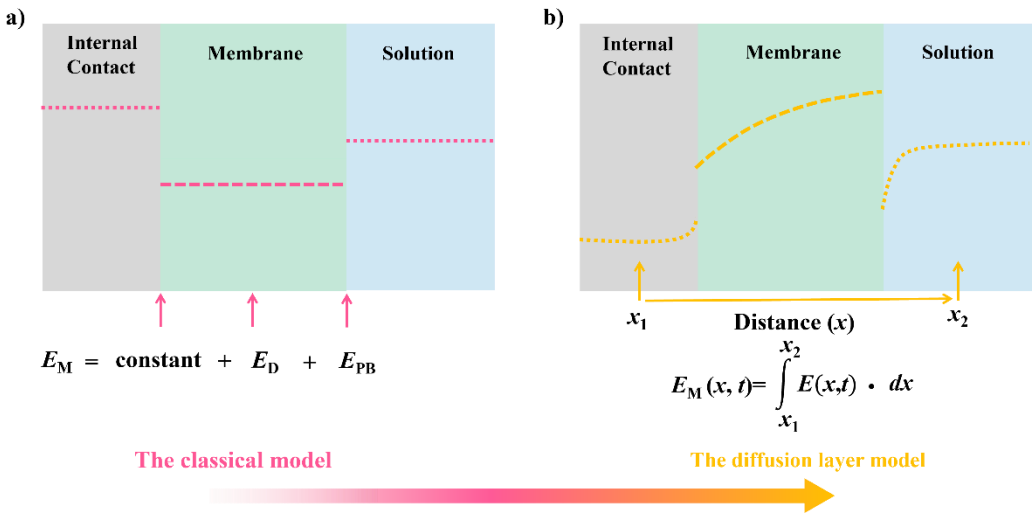

Figure 1. Schematic representation of **(a)** the classical model; **(b)** the diffusion layer model.

Potentiometry is an analytical detection method based on electrochemical principles. Its core lies in measuring the potential difference (*i.e.*, battery electromotive force) between the working electrode and the reference electrode, thereby enabling quantitative analysis of the target chemical substance. This measurement is typically conducted in an open-circuit state, based on the thermodynamic equilibrium process, and follows the theoretical framework of the Nernstian equation. According to this equation, a quantitative relationship can be established between the battery electromotive force and the activity of substances at the electrode-solution interface.

Based on this principle, ISEs achieve selective detection and precise quantification of the activity of target ions by integrating membrane materials with specific recognition functions. The working process is as follows: when the ISE is immersed in a solution containing the ions to be measured, the membrane material interacts specifically with the target ions, resulting in an uneven distribution of charges on both sides of the membrane, thereby forming a stable interfacial potential at the

membrane-solution interface. This interfacial potential is the basis for the generation of the potential signal response.

According to the classical theoretical model (Figure 1a), the total potential (E_M) of ISEs is mainly composed of two parts. The first part is the interfacial potential (E_{PB}) formed at the interface between the sample solution and the ISM, and the second part is the diffusion potential (E_D) generated within the membrane due to ion migration. Additionally, this model includes a constant term to represent the potential contribution at the contact interface within the electrode. The above relationship can be expressed by the following Equation.

$$E_M = E_{PB} + E_D + \text{constant} \quad (1)$$

In the classical theoretical model, the phase boundary potential E_{PB} represents the selective migration process of ions at the solution-membrane interface, while the diffusion potential E_D indicates the diffusion behavior of ions within the membrane. To simplify the processing, in the subsequent equations, it is assumed that any constant terms are zero. The phase boundary-potential model is a classic theoretical framework for analyzing E_M. It is established based on the following two idealized assumptions. First, this model assumes that the E_{PB} dominates the overall response, that is, $E_M = E_{PB}$. This assumption ignores the migration effect within the membrane, and it is based on the premise that the kinetic parameters of all charged substances (such as ionic mobility) are equal. Based on this assumption, the E_D can be regarded as zero. This essentially means assuming that the membrane is electrically neutral except for the boundary region. In some cases, although E_D is not zero, since it remains constant, it can still be approximated to be negligible. Second, this model assumes that the sample-membrane interface is always in an electrochemical equilibrium state, that is, the chemical potential of any ion that can cross the interface is balanced by the E_M (referred to as the equilibrium potential). Additionally, the model also assumes that the potential and ion concentration in each contacting phase remain constant in space and time, except at the phase boundary, and the ion concentration does not change with position.

$$\tilde{\mu}_i = \mu_i + z_i F\varphi = \mu_i^0 + RT\ln(a_i) + z_i F\varphi \quad (1)$$

Under the classical theoretical framework, $\tilde{\mu}_i$ represents the electrochemical potential, μ_i is the chemical potential within the phase (denoted as μ_i^0 in standard conditions), z_i is the valence of the ion, a_i is the ionic activity, φ is the ionic potential within the phase (*i.e.*, the internal potential), R is the ideal gas constant, T is the thermodynamic temperature, and F is the Faraday constant. Based on a series of idealized assumptions, the functional relationship between the E_{PB} and the ionic concentration (c_i) can be derived. These assumptions include that ion is the only ion capable of crossing the interface (ideal permanent selectivity assumption), the ion transfer process is rapid and reversible (infinite kinetics assumption). The two contacting phases have significantly different chemical properties and are completely immiscible (ideal immiscibility assumption). The single ionic activity a_i is used instead of the average ionic activity, and it is approximately assumed that the activity equals the concentration ($a_i = c_i$, ideal phase assumption). The solvent cannot be transported through the membrane (solvent impermeability assumption). Applying the Equation (2) to each phase and based on the condition of electrochemical equilibrium between phases where $\tilde{\mu}_i$ is equal and the chemical potentials of each phase are significantly different, after separating the electrical term from the chemical term, the Nernst equation satisfied by the ionic sensor interface potential difference can be obtained.

$$E_M = E_{PB} = \frac{RT}{z_i F} \ln k_i + \frac{RT}{z_i F} \ln \frac{c_i}{\bar{c}_i} \quad (2)$$

In the equation, c_i represents the concentration of ion i in the solution (mol/dm^3), $\bar{c}_i$ represents the concentration of ion i in the membrane phase (mol/dm^3), and the ion distribution constant k_i is defined as $\exp[(\mu_i^0 - \bar{\mu}_i^0) / RT]$, where μ_i^0 and $\bar{\mu}_i^0$ are the standard chemical potentials of ion i in the solution phase and the membrane phase, respectively. Based on the ion sensor response theory model proposed by Nikolskii [55], when considering an electrolyte solution system containing the main ion ($i = H^+$) and the monovalent interfering ion ($j = Na^+$), theoretical derivation yields the general mathematical expression of the sensor response as follows.

$$E_M = E_{PB} = \frac{RT}{z_i F} \ln k_i + \frac{RT}{z_i F} \ln \frac{c_i}{\bar{c}_i} = \frac{RT}{z_i F} \ln k_i + \frac{RT}{z_i F} \ln \left(\frac{c_i (\bar{c}_i + \bar{c}_j)}{\bar{c}_i (\bar{c}_i + \bar{c}_j)} \right) = \frac{RT}{z_i F} \ln k_i + \frac{RT}{z_i F} \ln \left(\frac{c_i + \frac{c_i \bar{c}_j}{\bar{c}_i}}{\bar{c}_i + \bar{c}_j} \right) = \frac{RT}{z_i F} \ln k_i + \frac{RT}{z_i F} \ln \frac{c_i + k_{i,j} c_j}{\bar{c}_i} = \text{constant} + \frac{RT}{z_i F} \ln (c_i + k_{i,j} c_j) \quad (4)$$

In the equation (4), $k_{i,j}$ represents the selectivity coefficient of the ion exchange reaction ($\bar{i^+} + j^+ = i^+ + \bar{j^+}$).

$$k_{i,j} = \frac{k_j}{k_i} = \frac{c_i \bar{c}_j}{c_j \bar{c}_i} \quad (5)$$

In the response model of the ISE, it is assumed that the total concentration of ions in the membrane phase remains constant, that is, the concentration $\bar{c}_i$ of the main ion i in the membrane phase and the concentration $\bar{c}_j$ of the interfering ion j in the membrane phase sum to a constant value. Based on this constant condition, the response of the ISE exhibits a typical Nernst correlation, and the working potential is linearly related to the logarithm of the activity of the ion to be measured in the solution (Equation (4)). In the electrochemical measurement system, by detecting the potential difference formed between the working electrode and the reference electrode in the electrolyte, the total electromotive force of the battery composed of these two electrodes can be obtained.

$$E = E_M - E_R = \text{constant} + \frac{RT}{z_i F} \ln (c_i + k_{i,j} c_j) - E_R = E^0 + k \ln c_i \quad (6)$$

Under standard conditions, the theoretical value of the proportionality constant k in the Nernst equation is $0.059/z_i$ (z_i is the ionic charge number). This theoretical relationship indicates that the establishment of the open-circuit potential (OCP) is entirely determined by the thermodynamic equilibrium of the system, and its response signal only depends on the concentration (or activity) of the target analyte, while showing strong resistance to external influencing factors. From a theoretical perspective, potentiometry has the following significant advantages: its potential response is independent of the apparent area and geometric size of the electrode; in *in vivo* analysis applications, compared with amperometry and voltammetry, it is significantly less affected by non-specific protein adsorption. These characteristics make potentiometry particularly suitable for in-situ analysis in complex biological systems.

2.2. The application of ISE in in vivo analysis

As a new generation of potentiometric sensors, SC-ISE has shown significant advantages over traditional liquid-contact ISEs. This sensor is easy to store and maintain, is insensitive to changes in external pressure, has low temperature dependence, and is more conducive to the flexible and miniaturized design and assembly of its structure [49,56]. These features make it have broad application prospects in *in vivo in situ* analysis. This article mainly introduces the application of SC-ISE in *in vivo* analysis. The core technical challenge of this sensor lies in the development of the transducer layer material. From the perspective of working principle, the transducer layer can convert the ion concentration signal into an electronic signal, thereby stabilizing the potential at the interface between the conductive substrate and the ISM, and accurately converting the ion signal to the electronic signal. This mechanism has become the standard working model of SC-ISE, ensuring the sensor has stable operational performance and good signal reproducibility. Currently, the ion-electron transduction principle of the transducer layer material can be roughly divided into two categories. One category forms a double-layer capacitance similar to an asymmetric capacitor between the transducer layer and the ISM, with the charges on both sides being the charges carried by the target ions passing through the ISM and the electronic charges formed by electrons or holes in the transducer layer. The size of this interface capacitance depends on the total charge in the double layer. The other principle is based on the redox reaction occurring in the transducer layer to achieve reversible ion-electron transduction, which usually involves the analyte ion or its hydrophobic counterion. It can be seen that the transducer layer is still a necessary component for regulating the charge transfer at the interface and further stabilizing the potential. An ideal transducer layer should have a large redox capacitance or double-layer capacitance to promote the reversible transduction of ions to electrons, be relatively hydrophobic to reduce the formation of a water layer at the contact interface between the sensitive membrane and the conductive substrate, and should not undergo side reactions [57]. So far, the most commonly used transduction layers mainly include conducting polymers (CPs) [58,59], carbon-based materials [60,61], and other functional nanomaterials [62–64]. According to the above classification method, this paper reviews the applications of three different types of SC-ISEs in *in vivo* analysis of brain neurochemistry.

Since their discovery in the late 1970s, CPs have rapidly attracted widespread attention in the field of analytical electrochemistry, especially represented by polypyrrole (PPY) [65], poly (3-octylthiophene) (POT) [66], polyaniline (PANI) [67], and poly(3,4-ethylenedioxythiophene) (PEDOT) [68]. From the perspective of the application of SC-ISE transduction layers, the core advantage of CPs lies in their unique hybrid conductive properties, which simultaneously possess both electronic and ionic conductive capabilities. This dual conductive mechanism enables CPs to efficiently convert ionic signals into electronic signals through redox reactions and ion transfer processes, thereby significantly improving the stability of sensors [69–72]. Moreover, the high redox capacitance characteristic of CPs helps to generate stable potential signals, which effectively overcomes the technical limitation of traditional electrodes that can only achieve a small current under zero current conditions.

This provides an important technical means for studying physiological parameters related to neurological phenomena such as spreading depolarization (SD). Veder *et al.* [73] successfully prepared a solid-state K^+ selective electrode in the POT film through electrochemical polymerization. The innovation of this electrode lies in that the doped ClO_4^- anions undergo an oxidation reaction with POT,

effectively promoting the ion-electron exchange process at the interface and enhancing the electronic conductivity. This mechanism not only ensures the stability of the interface potential but also provides a guarantee for the long-term stability of the electrode potential.

Odijk *et al.* [74] developed a SC-ISE based on a PEDOT transduction layer for selective detection of K^+ levels in the living mouse brain. Due to the low pH sensitivity of PEDOT and by comparing the conductive polymer layers prepared by different electro-deposition methods, it was found that the conductive polymer layer prepared by cyclic voltammetry had significantly better anti-interference performance against O_2 than those prepared by potentiostatic or galvanostatic techniques. Therefore, this probe exhibited excellent anti-interference performance against O_2 and pH changes. Based on these advantages, the probe successfully achieved synchronous monitoring at multiple depths and locations in the brain of living animals.

Tian *et al.* [28] developed a novel electrochemophysiological microarray (ECPM) for real-time quantitative detection of dynamic changes in multiple electrolyte ion concentrations in deep brain regions of freely moving rats (Figure 2a,b). Specifically, Figure 2a depicts the 5-channel ion-selective microelectrode array (5-ISMEA), which is assembled by integrating a K^+- selective microelectrode (K^+-ISME), a Ca^{2+}-ISEM, a Na^+-ISEM, a H^+-ISME and an inner-reference electrode for simultaneous multi-ion detection. Figure 2b illustrates an M-ISMEA was constructed by 7 responsive K^+-ISMEs (or Ca^{2+}–ISMEs, Na^+-ISMEs, H^+-ISMEs) and an inner-reference electrode for mapping and sensing of individual K^+ (or Ca^{2+}, Na^+, pH) in different regions of rat brain. The research team used electrochemical deposition technology to prepare a poly(3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) composite conductive film on the surface of the array electrodes, and then successively modified the ISM of Na^+, Ca^{2+}, K^+ and H^+ to construct a multifunctional sensing interface. Through OCP measurement technology, this sensor can simultaneously achieve specific detection of the four target analytes. In addition, based on the potentiometric working principle, this ECPM has unique advantages that are compatible with electrophysiological detection systems, enabling simultaneous monitoring of chemical signals and recording of neuronal electrical activities without mutual interference (Figure 2c). This feature provides an important technical platform for simultaneous neurochemical and electrophysiological studies. Peng *et al.* [75] developed a fiber potassium ion sensor (FKS). By enhancing the hydrophobicity of the transduction layer PEDOT:PSS, the interface stability between it and the potassium ISM was improved, effectively suppressing the formation of a water layer and ensuring the reliability of ion migration during long-term use (Figure 2d). After being implanted in the mouse brain, the FKS could stably monitor the dynamic changes of extracellular potassium ions under various physiological states, including anesthesia, forced swimming, and tail suspension (Figure 2e,f). Based on this sensor, the research group was able to track the fluctuations of extracellular K^+ associated with the progression of depressive behavior over several months, providing a new biochemical approach for the study of chronic neuropsychiatric diseases.

Compared with CPs that rely on redox reactions to achieve reversible conversion of ions and electrons, carbon materials have unique advantages as transduction layer materials. They not only possess excellent intrinsic conductivity, but also exhibit good chemical inertness to O_2, light, and redox substances. The ion-electron transduction mechanism of carbon materials relies on the double-layer capacitance response, which makes them have unique application value in SC-ISE. Therefore, how to effectively improve the double-layer capacitance has become the core scientific issue in the research of

carbon-based SC-ISE. Kozma *et al.* [76] innovatively covalently functionalized multi-walled carbon nanotubes (MWCNTs) with a chemically stable redox molecule (2,2,6,6-tetramethylpiperidin-1-yl) oxyl as the transduction layer, and successfully developed a new potassium ISE. This sensor based on functionalized nanomaterials effectively solved the common problem of potential drift in traditional SC-ISE and showed excellent electrochemical stability.

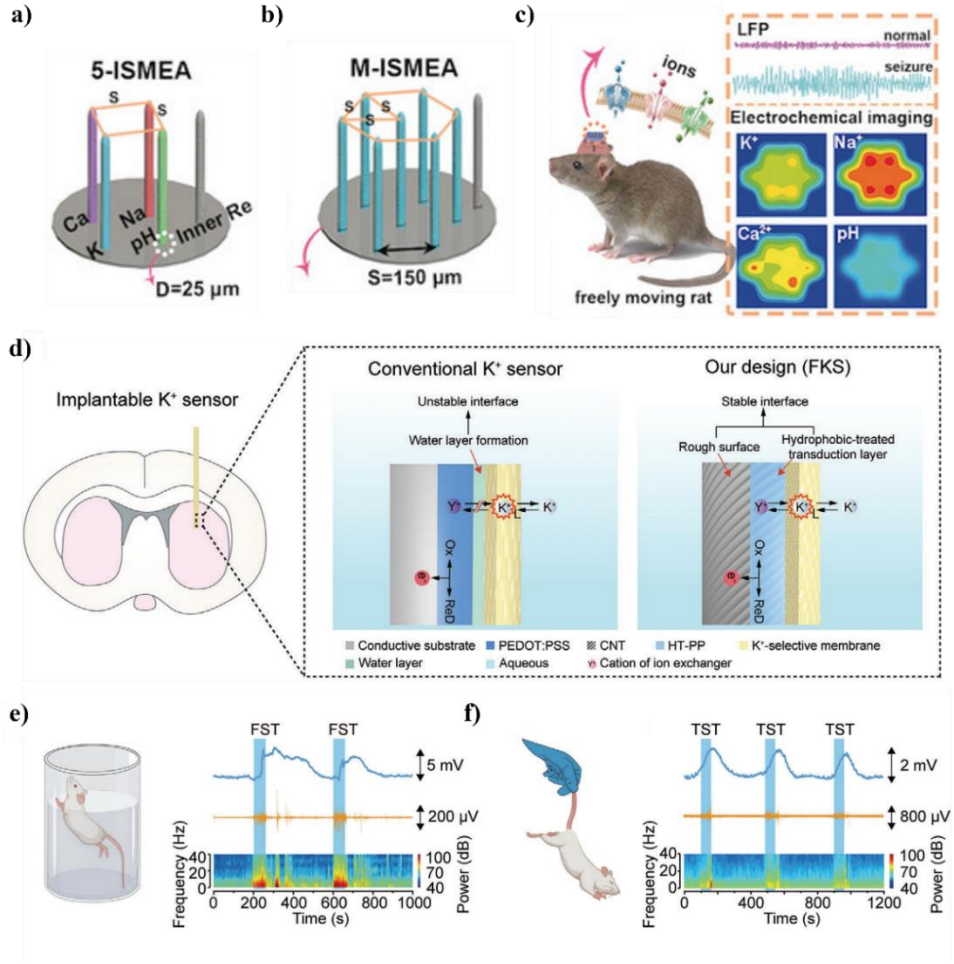

Figure 2. Schematic structures of **(a)** 5-channel 5-ISMEA and **(b)** 8-channel K^+-ISMEA (or Ca^{2+}-ISMEA, Na^+-ISMEA, H^+-ISMEA); **(c)** Local field potential (LFP) signals recorded in a live rat brain upon seizure and the developed ECPM for real-time mapping of multi-ions in the brain; **(a–c)** from reference [28]. Reprinted with permission. Copyright 2020 Wiley-VCH; **(d)** Interface design of the conventional K^+ sensor (left) and the FKS (right); **(e)** Schematic illustration and recordings of the forced swimming test (FST); **(f)** Schematic illustration and recordings of the tail suspension test (TST); **(d–f)** from reference [75]. Reprinted with permission. Copyright 2023 Wiley-VCH.

As shown in Figure 3a–c, the group of Mao applied hollow carbon nanospheres (HCNs) to the transduction layer construction, significantly enhancing the charge transfer efficiency between the ISM and the conductive substrate [57]. The use of HCNs fundamentally improved the signal stability of the sensor and minimized the potential drift of ISE. The transduction layer constructed with three layers of HCNs significantly improved the performance of Ca^{2+}-ISE and controlled the signal drift during the

detection process within a minimum range. Using this electrode to monitor the Ca^{2+} dynamics in the cerebral cortex of rats. After inducing SD through local electrical stimulation, it was observed that the extracellular Ca^{2+} concentration in the rat cortical cells showed significant fluctuations, with a decrease of 50% ± 8% compared to the baseline level. This achievement provides a new method for the miniaturization and real-time monitoring of ion dynamics in the living brain using SC-ISE. In the same year, this team [27] used graphdiyne oxide (GDYO) for the first time as the transduction layer material and combined with MnO_2 as an auxiliary material (Figure 3d), successfully developing the K^+-ISE. Experimental results confirmed that the unique molecular structure and hydrophobic properties of GDYO effectively inhibited the formation of the interfacial water layer, significantly improving the electrode's potential stability (Figure 3e,f). The prepared GDYO-MnO_2 composite transduction layer K^+-ISE exhibited excellent performance characteristics, not only having high selectivity but also maintaining good long-term stability, and could be effectively applied to the detection of K^+ in animal-level experiments. Additionally, the preparation method using GDYO as a solid-contact material demonstrates good universality features, can be extended to various ISE systems, and does not require complex processing procedures, providing new opportunities for the real-time monitoring of ion concentrations in the nervous system.

In addition to CPs and carbon materials, researchers have also proposed some promising transducer layer materials. Metal oxide nanoparticles offer a new alternative to obtain all solid-state ISEs. They are relatively cheap and readily available material. Pietrzak *et al.* [63] used different metal oxide nanoparticles as SC to construct potassium-sensitive ISEs. The slope of the standard curve of the modified electrode was slightly higher than that of the unmodified electrode. The nanoparticle-modified electrode exhibited better stability and potential reversibility, and the response time of the electrode was very fast. The electrode with ZnO nanoparticles also showed a very long lifespan, as they remained functional and maintained a very good slope even after 5 months. Qin *et al.* [77] evaluated the feasibility of MoO_2 microspheres as transducer layers. The MoO_2 microspheres were synthesized through a mild process by reducing MoO_3 nanobelts in isopropanol solvent. Compared with the coated wire electrode, the introduction of MoO_2 as an ion-electron transducer resulted in a SC-ISE with lower resistance and larger double-layer capacitance. Moreover, light, O_2, and CO_2 did not significantly affect its detection, and at the same time, this material effectively suppressed the formation of a water layer at the interface between the ISM and the conductive substrate, proving that MoO_2 microspheres can be good candidates for new transducer layers in SC-ISEs as metal analogues. In recent years, MXenes, a class of two-dimensional (2D) transition metal carbides and nitrides, have attracted significant attention due to their high specific surface area, large double-layer capacitance, and high metallic conductivity. Zeng *et al.* [64] utilized MXene ($Ti_3C_2T_x$ and Ti_2CT_x) nanosheets as ion-to-electron transducers for Ca^{2+}-ISEs. Electrochemical characterization indicated that the MXene-modified electrode had a high double-layer capacitance and rapid electron transport capability, enhancing the ion-electron transduction efficiency of SC-ISE and showing great application potential in ion sensing. Moon *et al.* [78] developed a novel dual microsensor capable of simultaneously monitoring the concentration changes of NO and K^+. This sensing device employed an amperometric/potentiometric dual-mode detection principle and contained two independent functional units: one was based on the direct oxidation reaction of NO, achieving quantitative analysis of NO by measuring the oxidation current; the other was a solid-state K^+-ISE with Ag/AgCl as the transducer layer for potentiometric detection of K^+. The researchers applied this sensor

to a 4-aminopyridine-induced acute epilepsy model and successfully recorded the dynamic changes of NO and K^+ in the deep brain tissue of rats during epileptic seizures.

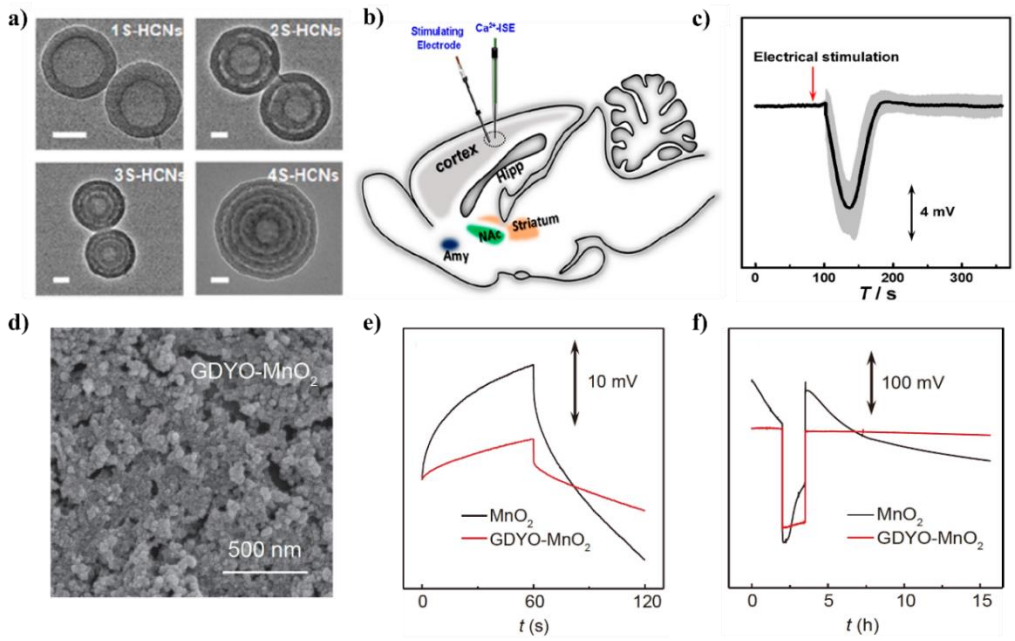

Figure 3. SC-ISEs with carbon-based materials as conducting layers for *in vivo* analysis. **(a)** Transmission electron microscopy (TEM) images of different shells of HCNs (shells 1–4). scale bar, 100 nm; **(b)** The Ca^{2+}-ISE for real-time monitoring of Ca^{2+} in the rat cortex during the SD process; **(c)** The occurrence of SD induced by local electrical stimulation leads to a decrease in extracellular Ca^{2+}. **(a–c)** from reference [57]. Reprinted with permission. Copyright 2019 American Chemical Society; **(d)** SEM image GDYO-MnO_2; **(e)** Chronopotentiograms of K^+-ISEs prepared with MnO_2 and GDYO-MnO_2 as the SC in 0.1 M KCl solution; **(f)** Water layer test for K^+-ISEs with the SC of MnO_2 and GDYO-MnO_2. **(d–f)** from reference [27]. Reprinted with permission. Copyright 2019 Science China Press and Springer-Verlag GmbH Germany, part of Springer Nature.

In addition to the aforementioned single-material system, in recent years, the research focus on composite materials in related fields has significantly increased, and a large number of new composite materials have been developed and reported. Composite materials usually possess superior mechanical, thermal, electrical, optical and chemical properties compared to single components. Leveraging this advantage, functional materials with more excellent comprehensive performance can be prepared, such as higher specific capacitance, lower impedance, larger specific surface area and stronger hydrophobicity, *etc.* Boeva *et al.* [79] for the first time used a composite material composed of polyaniline (PANI) and graphene as the contact layer of the Ca^{2+}-selective solid-contact electrodes (CaSCISEs). The contact layer maintains the ion-to-electron transduction which is characteristic for the electrically conducting polymers (ECP), but in addition, graphene improves the reproducibility of the standard potential of the SC-ISEs compared to the neat PANI based electrodes and increases the hydrophobicity of the transducer which counteracts the water layer formation. This work reveals that the incorporation of few-layer graphene in the transducer layer improved also the initial potential stability and the response

characteristics of the CaSCISEs due to the electrocatalytic effect of the graphene-ECP composite, which facilitates the electron transfer at the transducer/substrate interface.

Zeng *et al.* [80] introduced polydopamine on the surface of carbon fibers (CFs) through self-polymerization, and then in-situ grew zeolitic imidazolate frameworks as the precursor of carbon-based catalysts. Finally, through one-step pyrolysis, they successfully prepared nitrogen/carbon (N/C)-functionalized CFs with hydrophobic and rough surface characteristics on a large scale (Figure 4a,b). The obtained N/C layer was used as the transduction layer of the H^+-ISE, which could effectively suppress the potential drift caused by the formation of an internal water layer and contact surface polarization, thereby achieving stable detection of H^+ concentration in the brain (Figure 4c,d). The group of Qin [81] used the covalent organic framework@reduced graphene oxide (rGO) composite material as an ion-to-electron transducer to develop a SC-Cd^{2+}-ISE. The composite can be synthesized through the polycondensation of 1,3,5-triformylphloroglucinol (TFP) and 2,6-diaminoanthraquinone (DAAQ) on the rGO nanosheets, which shows high capacitance and good redox-active properties. Moreover, the DAAQ-TFP@rGO-based Cd^{2+}-ISE exhibits excellent reproducibility, is unaffected by light or gas interference, and eliminates the formation of an aqueous layer between the sensing membrane and the composite layer. These results demonstrate that the DAAQ-TFP@rGO composite holds great promise for the construction of calibration-free SC-ISEs. In conclusion, the incorporation of composite materials represents a major advancement in the development of potential sensors. Driven by ongoing progress in materials engineering, this field has fostered the continuous innovation and development of multicomponent functional materials.

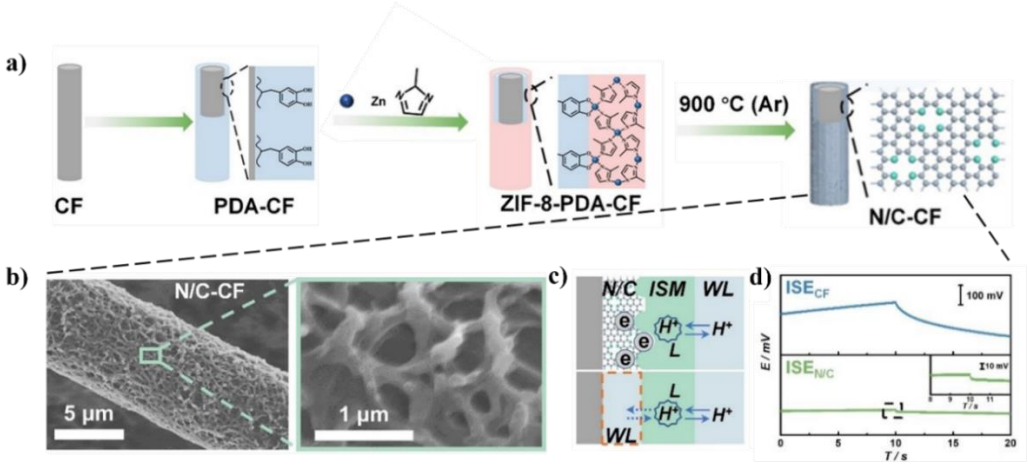

Figure 4. Modification and performance of N/C-CF-based H^+-ISE. **(a)** Schematic of *in situ* engineering strategy for preparing N/C functionalized CF; **(b)** SEM image of N/C-CF; **(c)** Schematic mechanism of H^+-ISE microsensor with (upper) and without (bottom) N/C as the transduction layer; **(d)** Chronopotentiometry results of ISE_{CF} (upper) and $ISE_{N/C}$ (bottom) in 0.1 M HCl with the applied current of + 0.1 nA for 10 s and then −0.1 nA for 10 s. **(a–d)** from reference [80]. Reprinted with permission. Copyright 2024 Wiley-VCH.

In SC-ISEs, the design strategy of the ISM has long been a central research focus. On one hand, leakage of ISM components into the sample solution not only results in performance degradation or even complete failure of SC-ISEs, but also leads to sample contamination. Notably, ionophores employed in ISMs are not only costly but also toxic [82,83], and their handling during electrode preparation and

application may compromise the reliability of *in vivo* detection. On the other hand, hydration interactions at the SC-ISM interface can induce severe potential drift in SC-ISEs. Although enhancing the hydrophobicity of the SC represents an effective approach, the intrinsic hydrophilic nature of ISMs makes it difficult to fully suppress transmembrane water transport, especially during long-term analytical measurements and *in situ* monitoring. Given the aforementioned challenges, the design and construction of ISM-free SC-ISEs hold great promise and are highly significant for *in vivo* sensing applications.

Zhang's group [84] develop a flexible fiber-based ion-selective sensors (ff-ISEs) for long-term monitoring of ions in rat brain, in which zeolite imidazolate framework-8 (ZIF-8) nanoparticles incorporated with ionophores are used for selective ion recognition and flexible polyvinyl alcohol fibers sputtered with gold nanoparticles are used as the soft electrode substrate (Figure 5a). By utilizing the porous structure and channels of ZIF-8 and encapsulating the ionophores within it to form an ISM-free structure, this design effectively prevents the leaching of the ionophores and eliminates undesired water layers (Figure 5b), thereby improving the long-term operational stability of the ISE *in vivo* (Figure 5c,d). Papp *et al.* [85] reported the synthesis and analytical application of the first Cu^{2+}-selective synthetic ion channel based on peptide-modified gold nanopores. By chemically modifying solid-state nanopores to mimic biological ion-selective filters, they further demonstrated its promising applications in synthetic chemistry and analytical sensing. As all functional components are immobilized on a supporting nanoporous, this system effectively circumvents the leaching issue commonly encountered in conventional ionophore-based ISEs. Furthermore, with a few exceptions the selectivity of the peptide-based ISEs proved to be better than that of Cu^{2+}-ionophores in conventional plasticized PVC membranes.

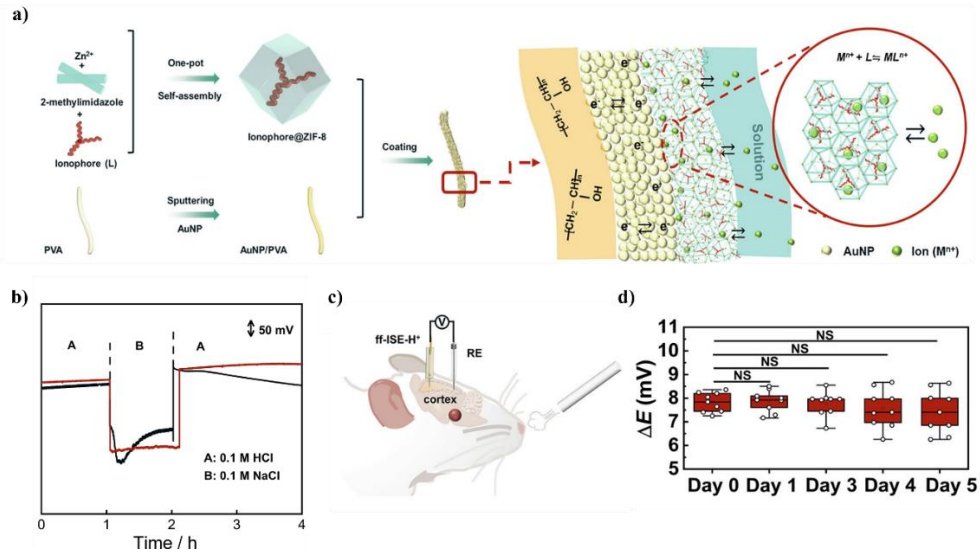

Figure 5. Mechanism and *in vivo* sensing performance of ff-ISEs. **(a)** Schematic illustration of preparation and response mechanisms for the ff-ISEs; **(b)** A water layer test was carried out by continuously recording the potential responses of the ff-ISE-H^+ and the conventional H^+-ISE; **(c)** Schematic illustration of *in vivo* sensing of H^+ in rat brain; **(d)** Potentiometric response of the ff-ISE-H^+ to H^+ at different days. **(a–d)** from reference [84]. Reprinted with permission. Copyright 2025 Wiley-VCH.

So far, apart from CPs, carbon materials, and metal nanoparticles, all of which can form asymmetric capacitors via redox or double-layer capacitance, the introduction of composite materials represents a

significant breakthrough in the development of potentiometric sensors. These composite materials endow electrodes with superior performance and exhibit better application effects than single-component materials. However, due to differences in the properties of functional materials, preparation methods, and experimental conditions, the same material may yield inconsistent results. Currently, there is a lack of universal standards for transduction layer materials used in fabricating SC-ISEs. Therefore, it is necessary to improve testing and evaluation standards to promote the standardized development of SC-ISEs, and developing more versatile transduction layer materials remains a key direction in the field of potentiometric sensing. Meanwhile, most current research on SC-ISEs still focuses on electrode structures integrated with ISMs, overlooking the high cost of ISMs and their unavoidable impact on potential stability. In contrast, ISM-free SC-ISEs possess numerous advantages, including high performance, low cost, long service life, and the absence of a water layer effect. Nevertheless, their development is still in its infancy, suffering from a shortage of functional materials and insufficient theoretical research. In the future, efforts should focus on enhancing their sensing performance and exploring their selectivity and response mechanisms to provide theoretical support for practical applications.

Moreover, the response mechanism of the aforementioned ISEs is based on the classical phase boundary model, which assumes that the membrane/solution interface reaches thermodynamic equilibrium. This is also the most widely adopted theory for describing the response of ISMs. Under this assumption, the electrode can exhibit a thermodynamic equilibrium response that conforms to the Nernstian behavior. However, this model ignores electrochemical migration and time-dependent effects, making it difficult to fully describe the spatiotemporal dynamic characteristics of the sensor response [86]. With a deeper understanding and theoretical modeling of the potential response mechanism of ISEs, researchers have successively proposed more advanced non-equilibrium models to describe their response behavior. In recent years, non-equilibrium electrochemical methods such as voltammetry, cyclic and normal pulse voltammetry have been used to characterize, analyze, and fine tuning of ion fluxes across the polymeric membrane; ISEs based on dynamic electrochemical regulation have also given rise to new sensor design concepts such as chrono-potential method, thin-layer coulometry, and thin-layer membranes for stripping ion-transfer analysis [37,51,53]. The Bakker research group is still one of the leading teams in this field to date. Currently, the potential of non-equilibrium measurement–based potentiometric sensing strategies has been demonstrated in biological detection, permitting the quantification of small molecules, DNA, enzymes, proteins, and other biological targets [50]. Nevertheless, owing to the intricate microenvironment in the brain, the vast majority of related studies remain restricted to *in vitro* sample analysis or wearable device applications. With the incorporation of novel functional materials and rational structural design of sensors, dynamic electrochemical approaches employing polymer membranes exhibit promising prospects for *in situ* brain sensing and merit further in-depth investigation.

3. The basic principle of GRP and its application in *in vivo* analysis

3.1. The basic principles of GRP

Traditional potentiometric detection based on ISEs exhibits significant limitations in analyzing redox-active species. To address this challenge, Mao's group proposed an innovative detection strategy named GRP, which leverages the working principle of a galvanic cell to achieve efficient detection of electroactive neurochemicals. This sensor comprises a positive electrode (cathode) and a negative electrode

(anode), which are connected via a potentiometer to form a complete electrochemical circuit (as shown in Figure 6a) [20,87]. In this system, the reduced species R undergoes oxidation at the anode surface, and its electrode potential E_a is expressed by Equation (7). Meanwhile, the oxidized species O′ undergoes reduction at the cathode surface, with the corresponding electrode potential E_c given by Equation (8). The overall reaction process for these electrode reactions can be described by Equation (9).

$$\text{Anode: aR} \rightleftharpoons \text{bO} + \text{ne}^- \ (\text{E}_a) \tag{7}$$

$$\text{Cathode:}\ c\mathbf{O'} + n\text{e}^- \rightleftharpoons d\mathbf{R'}\ (E_c) \tag{8}$$

$$\text{Overall reaction:}\ a\mathbf{R} + c\mathbf{O'} \rightleftharpoons b\mathbf{O} + d\mathbf{R'}\ (E_{OC}) \tag{9}$$

Under open-circuit conditions, the two electrodes in this electrochemical system are nearly in equilibrium. Accordingly, the relationship governing electrode potentials can be approximately described by the Nernstian equation as follows:

$$E_a = E_a{}^{\circ'} + \frac{RT}{n\text{F}} ln \frac{C_O^{*b}}{C_R^{*a}} \tag{10}$$

$$E_c = E_c{}^{\circ'} + \frac{RT}{n\text{F}} ln \frac{C_{O'}^{*b}}{C_{R'}^{*d}} \tag{11}$$

In the above expressions, $E_a{}^{\circ}$ and $E_c{}^{\circ}$ correspond to the apparent formal potentials of the negative and positive electrode reactions, respectively. Here, C_O*, $C_{O'}$*, C_R*, $C_{R'}$* denote the interfacial concentrations of the oxidized species O, oxidized species O′, reduced species R, and reduced species R′ at the electrode solution interface. The parameter *n* stands for the number of electrons transferred in the reaction, R is the universal gas constant, T is the thermodynamic temperature, and F represents the Faraday constant. From these parameters, the OCP *(Eoc)* of the system can be expressed as follows. Equation (12) reveals that the OCP of the GRP sensing system exhibits a favorable linear correlation with the logarithm of the analyte concentration.

$$E_{OC} = E_c - E_a = E_c{}^{\circ'} - E_a{}^{\circ'} + \frac{RT}{n\text{F}} ln \frac{C_R^{*a} C_{O'}^{*c}}{C_O^{*b} C_{R'}^{*d}} \tag{12}$$

This characteristic relationship forms the theoretical foundation for quantitative analysis using GRP. In contrast to conventional redox potentiometric sensing, the GRP approach treats the assembly of the working (indicator) electrode and the reference electrode as an integrated electrochemical system. It not only requires a stable reference electrode potential but also emphasizes the potential correlation between the working and reference electrodes. This innovative design overcomes the limitations of traditional potentiometric methods, which only demand a stable reference potential without specifying the potential relationship between the two electrodes [20]. In practical applications, the GRP technique enables effective regulation of the working electrode polarization direction by engineering the electrochemical reaction pathway at the reference electrode, thus guaranteeing the stability of the measured signal [87].

3.2. The application of GRP in in vivo analysis

As an innovative platform for neurochemical sensing, the GRP system exhibits outstanding neuronal compatibility and extends the detection scope of potentiometry from ions to diverse redox-active

molecules. A prerequisite for constructing a GRP sensor is the occurrence of a spontaneous redox reaction ($E_c > E_a$). Only when molecular recognition occurs at the indicating electrode and an electrochemical circuit with a negative Gibbs free energy change is established, can the sensor generate a concentration-dependent E_{OC} response toward the analyte. Consequently, the GRP system operates under near-zero-current conditions, exhibiting high promise in minimizing the risk of current induced disturbance to neurons within the central nervous system [88]. Wu *et al.* [87] innovatively applied GRP sensors to *in vivo* and *in situ* detection, establishing a new strategy for this field. The researchers modified CFE surfaces with single-walled carbon nanotube (SWNT-CFE), taking advantage of the ability of SWNTs to lower the oxidation overpotential of AA, thereby enabling the spontaneous oxidation of AA. Meanwhile, laccase was immobilized on another CFE (Lac-CFE) to construct a catalytic site for oxygen reduction. Given that the oxidation potential of AA at the SWNT-CFE is lower than the reduction potential of oxygen at the Lac-CFE, this potential difference spontaneously drives the redox reaction (as illustrated in Figure 6b). The sensor displayed outstanding selectivity toward AA and effectively eliminated interference from other electroactive species, while its sensitivity remained unaffected by nonspecific protein adsorption. It was successfully employed in *in vivo* experiments, enabling accurate quantification of basal AA levels in the rat brain and real-time monitoring of AA concentration fluctuations during ischemia-reperfusion.

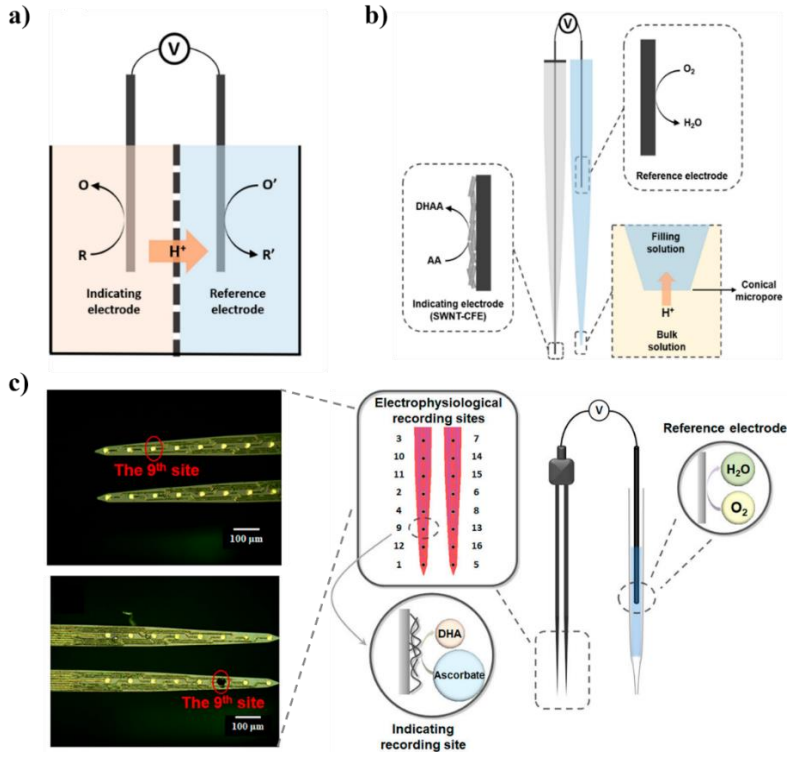

Figure 6. Configuration of GRP sensors and microelectrode arrays. **(a)** Schematic illustration of a prototype GRP sensor; **(b)** Schematic illustration of GRP sensor for *in vivo* measurement of AA. **(a, b)** from reference [87]. Reprinted with permission. Copyright 2018 American Chemical Society; **(c)** Schematic illustration of the GRP-based MEA sensor. In this setup, the 9th site at the MEA was selected as the indicating electrode, while all the other sites were selected as the electrophysiological recording sites. Photographs of the 9th site at the MEA before (top) and after (bottom) modification with SWNTs. **(c)** from reference [19]. Reprinted with permission. Copyright 2020 American Chemical Society.

Building on their previous work, Wei *et al.* [19] innovatively integrated GRP and electrophysiological recording onto a 16-site Au microelectrode array (MEA), one of which is for indicating the AA concentration while the others for single-unit activity assessment, as illustrated in Figure 6c. They modified each detection unit of the electrode array with single-walled carbon nanotubes to serve as the anode component of the GRP system, markedly improving the electrocatalytic oxidation efficiency toward AA. In this GRP system, platinum electrodes were employed as the cathode, forming a self-driven redox reaction system together with the functionalized anode. This sensing platform enables simultaneous acquisition of electrochemical and electrophysiological signals, with both signal outputs stable and free of mutual interference. It was successfully applied to achieve synchronous monitoring of AA concentration dynamics and neuronal electrophysiological activity during SD.

In the two-electrode system of the GRP sensor, the oxygen reduction process is usually designed as the cathodic reaction. Although a relatively stable and more positive electrode potential compared to the anode can be provided through reasonable electrode structure design (e.g., glass capillary encapsulation) and efficient oxygen reduction catalysts (e.g., platinum-based catalysts, laccase, *etc.*), thereby constructing a spontaneous redox process, this electrode structure is still relatively complex, and the cathodic potential and performance are difficult to regulate. Different from the two-electrode spontaneous polarization-based GRP sensor ($GRP_{1.0}$), the $GRP_{2.0}$ simultaneously undergoes electrochemical oxidation and reduction reactions at different positions of a single electrode, showing spontaneous polarization characteristics (Figure 7a). This sensor uses a single CF sealed with a micropipette, which respectively forms the outer anodic pole and the inner cathodic pole. When used for *in vivo* detection of neurochemical substances, the cathodic pole does not need to be directly implanted into the brain tissue, thereby avoiding interference such as oxygen insufficiency, pH disturbance, and mass crossover, and it is easier to effectively control the cathodic properties of the GRP system.

Yu *et al.* [89] first introduced a neuron-compatible method for *in vivo* neurochemical sensing by powering a single CF through spontaneous bipolar electrochemistry as a $GRP_{2.0}$ sensing platform. This research conducted a proof-of-concept using as AA as the model target. An artificial cerebral spinal fluid containing $K_3Fe(CN)_6$ was filled into a glass pipette, while the other electrode of the CF was immersed in the bulk solution containing the target molecule AA (as shown in Figure 7b). By functionalizing the surface of CFE with MWNTs to reduce the overpotential for AA oxidation, the redox reaction was driven to occur spontaneously, achieving the bipolar effect on a single CF. The study demonstrated that the single-CF-powered microsensor exhibited a good response, high stability and, more importantly, excellent neuronal compatibility. The sensing principle could be developed for *in vivo* monitoring of various neurochemicals in the future by rationally designing and tuning the electrochemical reactions at the two poles of the CF. Zhu *et al.* [90] developed a fouling-free $GRP_{2.0}$ system for 5-HT detection, composed of a 5-HT-responsive indicator electrode and a cathodic reference electrode embedded in K_2IrCl_6 solution (Figure 7c). In the presence of 5-HT, the bipolar system establishes a circuit with negative Gibbs free energy, enabling spontaneous generation of a concentration-dependent OCP response (Figure 7d). In contrast to conventional amperometric 5-HT sensors, the GRP-based 5-HT sensor exhibited a signal variation of less than 3% during 2-hour continuous measurements, revealing significantly enhanced stability. In situ Raman spectroscopy further confirmed that this sensor effectively minimizes electrode fouling. This platform offers a reliable strategy for monitoring various neurochemicals having significant fouling issues, thus advancing molecular-level understanding of brain

functions. Wei *et al.* [88] established a theoretical model to elucidate the mechanism by which the sort and concentration ratio of employed redox couples influence the stability of the cathode. Results demonstrated that when utilizing $IrCl_6^{2-/3-}$ at a 1:1 concentration ratio as the counterpart, the $GRP_{2.0}$ system not only exhibited outstanding E_{OC} stability but also displayed minimal electrode-to-electrode variation. When integrated with electrophysiological measurements, $GRP_{2.0}$ successfully captured robust DA release accompanied by bursts of neural firing during optical stimulation (Figure 7e). This work provides a new strategy for achieving stable *in vivo* sensing of neurochemical substances.

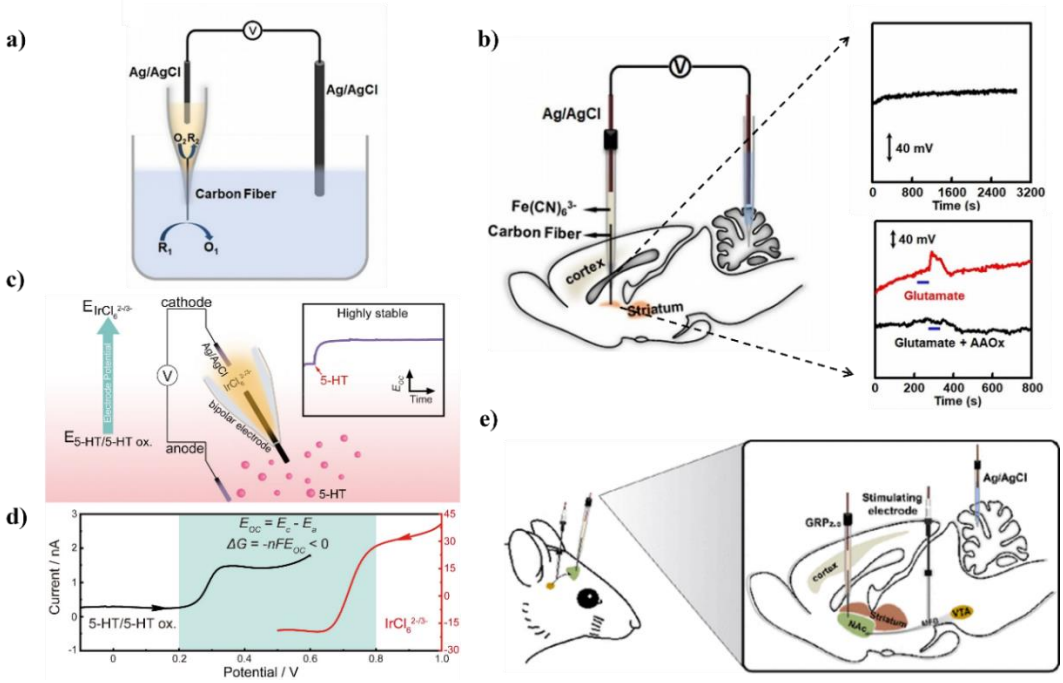

Figure 7. Designs and *in vivo* sensing performances of $GRP_{2.0}$ sensors. **(a)** Schematic illustration of a spontaneously powered single-electrode-based $GRP_{2.0}$ sensor; **(b)** *In vivo* sensing of the dynamics of AA with the $GRP_{2.0}$ sensing platform; **(a, b)** Reprinted with permission from reference [89]. Copyright 2020 Wiley-VCH. **(c)** Schematic illustration of a fouling-free $GRP_{2.0}$ system for 5-HT; **(d)** Current/voltage response of the anode (10 μM 5-HT, black curve) and of the cathode (1 mM $IrCl_6^{2-/3-}$, red curve); **(c, d)** from reference [90]. Reprinted with permission. Copyright 2023 Wiley-VCH. **(e)** Schematic illustration of the $GRP_{2.0}$ for *in vivo* monitoring DA release, it froms reference [88]. Reprinted with permission. Copyright 2023 American Chemical Society.

Currently, selective *in vivo* sensing of AA, H_2S, 5-HT, molecular oxygen, and other species has been realized using the GRP system [88–92]. To address interference from coexisting neurochemicals with similar redox potentials, these studies employed a formal potential ordering strategy to modulate heterogeneous electron-transfer kinetics, thereby enabling selective recognition of target analytes via controlled oxidation or reduction processes [93]. Beyond the synthetic electrocatalysts already utilized, including single-atom catalysts and carbon-based nanostructures, diverse biocatalysts such as enzymes offer extensive opportunities for the design of selective GRP sensors [94–97].

Lu *et al.* [98] proposed a concept of novel enzymatic GRP, which integrates the high selectivity of enzyme electrodes with the favorable biocompatibility and reliability of GRP sensors. As shown in

(Figure 8a,b), an enzymatic GRP sensing platform for glucose detection was constructed using flavin adenine dinucleotide-dependent glucose dehydrogenase as the recognition element and carbon black as the potential relay station to improve the response time. Employing E_{OC} as the signal output, this GRP biosensor exhibits rapid response toward glucose, high selectivity against O_2 and other neurochemical interferents, satisfactory stability, and excellent reversibility and antifouling properties during glucose sensing in the rat brain. These merits enable the enzymatic GRP biosensor to be applied for investigating brain metabolism. Furthermore, this approach can be extended to the *in vivo* detection of other neurochemicals with poor redox activity, offering a new platform for highly reliable *in vivo* biosensing. In addition to the enzymatic GRP biosensor, Ni *et al.* [99] integrated the selectivity and stability of phosphorothioate aptamers with the bipolar GRP system to specifically detect the dynamic changes of DA in the living rat brain (Figure 8c). This technology enhanced the biostability and eliminated the dependence on external polarization voltage, thereby constructing an aptamer-functionalized GRP (aptGRP) platform with high neural compatibility. Moreover, the aptGRP platform exerted negligible effects on neuronal activity, permitting real-time, simultaneous recording of DA dynamics and electrical signals across brain regions of living rats (Figure 8d). Zhu *et al.* [100] designed a aptGRP sensor with enhanced sensitivity and selectivity enables real-time monitoring of 5-HT in a mouse model of psychosocial stress. It reveals a distinct correlation between 5-HT release and social hierarchy, such that dominant mice display elevated 5-HT levels. These efficient and versatile aptGRP strategies will greatly advance toolbox for understanding molecular processes in the brain.

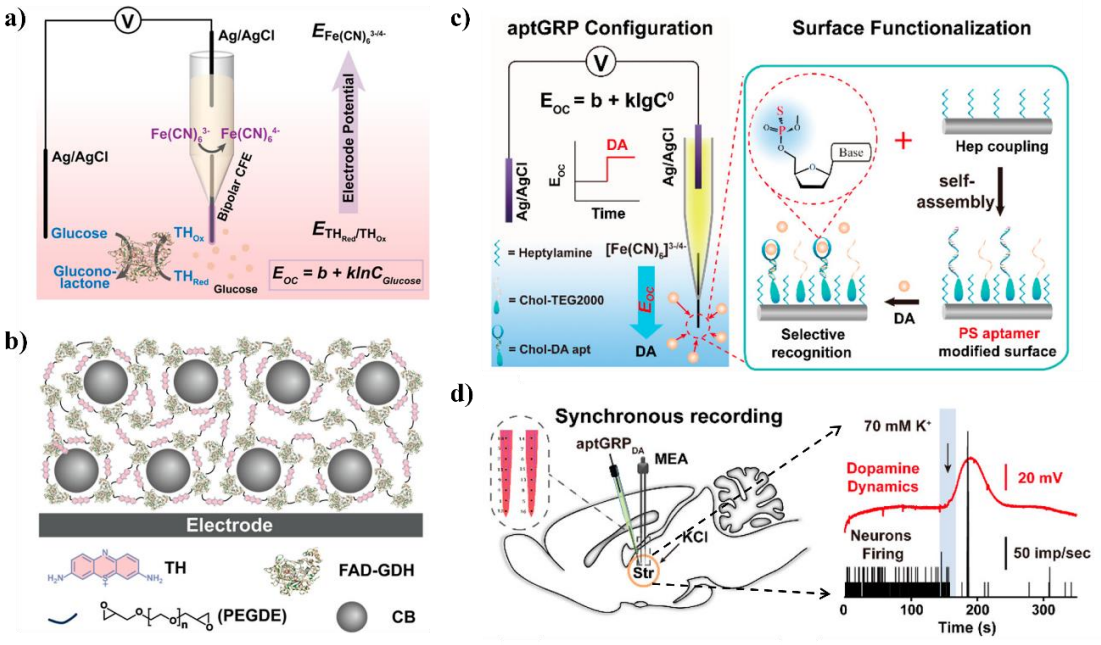

Figure 8. Construction and *in vivo* performance of enzymatic and aptamer-based GRP biosensors. **(a)** Schematic Illustration of the design of the enzymatic GRP Biosensor; **(b)** Schematic diagram of the composition of the Enzyme Electrode; **(a, b)** from reference [98]. Reprinted with permission. Copyright 2024 American Chemical Society; **(c)** Schematic of the aptGRP configuration and surface functionalization; **(d)** *In vivo* synchronous recording of E_{OC} response with aptGRP and electrophysiological recording by the 16-channel gold-based microelectrode arrays. **(c, d)** from reference [99]. Reprinted with permission. Copyright 2024 American Chemical Society.

With the introduction of the GRP strategy, the analytical scope of potentiometry has been extended from non-electroactive ions to the quantitative detection of electroactive neurochemicals. Nevertheless, the variety of neurochemicals detectable via the GRP principle remains rather limited to date. Moving forward, rational design and engineering of electrode interfaces and architectures will further broaden the detection spectrum of neurochemicals using the GRP method. Furthermore, this approach is anticipated to be synergistically combined with physiological techniques including electrophysiology, optogenetics, and neuroimaging, enabling a more comprehensive interrogation of brain neural activities and thus offering a novel technical route for the chemical analysis of complex neural processes *in vivo*.

4. Conclusions and prospects

With the advancement of SC-ISEs, the expanding library of nanomaterials, the diversification of sensor architectures, and the continuous emergence of novel sensing principles, potentiometric strategies based on implantable micro/nanoelectrodes have assumed an increasingly vital role in neurochemical research. Considerable efforts have been devoted to enhancing the sensitivity, selectivity, detection limit, operational lifetime, biocompatibility, and antifouling properties of such sensors, while also extending the scope of potentiometric detection beyond common ions. In addition, flexible SC-ISEs have been extensively employed to mitigate chronic shear stress, reduce foreign body responses, and ensure stable integration. Despite these remarkable advances, many aspects of potentiometric detection tailored for neural systems still require further development. Beyond exploring high-performance SC functional materials, there is an urgent need to develop novel membrane materials and ionophores, as well as to optimize fabrication protocols and conditioning processes. Furthermore, while SC-ISEs have achieved substantial progress in calibration-free and maintenance-free sensing, they remain in the early stages of practical translational implementation.

To further extend its application scenarios and improve detection performance, the new generation of potentiometric sensors is gradually evolving toward integration and intelligence [101]. By integrating with advanced electronic components, SC-ISEs enable wireless remote ion monitoring with more intelligent data acquisition and analytical capabilities. Meanwhile, the introduction of dynamic electrochemical protocols has transformed the sensing mechanism of SC-ISEs from traditional zero-current potentiometry to dynamic potentiometry with versatile readout modes. In addition, potentiometric sensors exhibit excellent neuron compatibility and do not interfere with the recording of other electrophysiological signals, making them highly suitable for the development of dual-modal detection techniques that combine electrochemical and chemical molecular signals. Such approaches allow simultaneous monitoring of electrical activity and molecular-level information, offering high complementarity and detection accuracy. On this basis, the construction of transformative multi-modal platforms integrating electrical, optical, and other sensing modalities is expected to break through the inherent limitations of single-modal detection, addressing constraints in detection range, spatiotemporal resolution, and accessibility, and enabling brain-wide analysis, multi-analyte monitoring, and remote operation. In recent years, artificial intelligence and machine learning have exerted transformative impacts across numerous cutting-edge disciplines, including potentiometric sensing [102,103]. Machine learning algorithms trained on large datasets can be employed to construct intelligent potentiometric biosensors, allowing accurate identification and quantitative analysis of target analytes in complex matrices [104,105]. Benefiting from real-time and continuous monitoring capabilities, machine learning

further facilitates the real-time recognition and quantification of target species by potentiometric sensors. Furthermore, the integration of implantable potentiometric microsensors with artificial intelligence and the Internet of Things offers new opportunities for real-time surveillance of animal diseases, visualization of health data, and timely implementation of preventive healthcare strategies.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used generative AI tools only to improve language and readability. Specifically, the authors used Doubao for language polishing only in substantial portions. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Investigation, Rantong Liu; writing—original draft preparation, Rantong Liu; writing—review and editing, Meining Zhang; supervision, Meining Zhang; project administration, Meining Zhang; funding acquisition, Meining Zhang. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Meining Zhang holds the position of Editorial board member for *Life Analysis* and has not peer reviewed or made any editorial decisions for this paper.

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