Review

In Vivo Electrochemical Biosensors: Technology and Personalized Medicine Go Hand in Hand

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Abstract: In vivo electrochemical biosensors (IVEBs) have emerged as pivotal tools in advancing personalized healthcare paradigms, particularly due to their exceptional capability for real-time tracking of dynamic physiological biomarkers. Their seamless integration into next-generation health monitoring platforms has not only revolutionized clinical diagnostics but also propelled the innovation of implantable sensing architectures, thereby redefining precision medicine strategies through continuous in situ bioanalytical measurements. This review highlights the latest advancements of IVEBs, including potentiometric, amperometric, and impedance biosensors, emphasizing their high sensitivity, specificity, and capability to function in complex biological environments. Additionally, this review discusses the limitations of current IVEBs, such as sensitivity, miniaturization, and applications of biodiversity. In future, researchers should use novel biocompatible nanomaterials and artificial intelligence algorithms to promote the development of IVEBs.

Keywords: in vivo; electrochemical biosensors; invasive and non-invasive; personalized medicine

1. Introduction

The global demographic shift towards aging populations and the escalating prevalence of chronic diseases have intensified the demand for real-time health monitoring technologies in modern healthcare systems [1–6]. These imperatives drive scientific efforts to develop continuous biomarker tracking platforms capable of enhancing clinical decision-making and patient quality of life [7–9]. In vivo electrochemical biosensors (IVEBs) emerge as a transformative paradigm, leveraging interdisciplinary advances in microelectronics, nanomaterial engineering, and wireless communication [10–14]. By enabling real-time quantification of critical physiological parameters, including glycemic levels [15], sweat electrolytes via multiplexed sensor arrays [16], and cortisol in tears [17], IVEBs hold particular promise for chronic disease management, preventive healthcare, and personalized therapeutic interventions. Such systems empower patients and clinicians to dynamically adjust treatment regimens through data-driven insights, thereby advancing precision medicine frameworks.

The operational principle of IVEBs relies on electrochemical transduction mechanisms (e.g., amperometric [18], potentiometric [19], impedimetric [20]) to achieve target analyte specificity across diverse biofluids [21]. Device miniaturization, exemplified by commercial continuous glucose monitoring systems [22,23], has facilitated clinical translation while maintaining analytical performance. The widespread adoption of smartphones [24] and micro/nano fabrication technology [25,26] has further facilitated the integration of IVEBs, enabling real-time and continuous health monitoring in vivo. IVEBs not only monitor conventional analytes such as glucose and cholesterol but also extend to the analysis of alternative biological fluids like sweat and tears, including electrolytes, metabolites, pharmaceuticals, and other related substances [27–30], expanding their applicability beyond traditional biofluids (blood [31], interstitial fluid [32]) to alternative matrices such as tissue [33], sweat [34], tears [29], saliva [35] and exhaled breath condensate [36]. These samples are rich in biomarker information, making them valuable for real-

time monitoring and disease diagnosis. Contemporary implementations utilize minimally invasive interfaces including microneedle arrays [37] and microelectrodes [31], which can be seamlessly integrated into wearable devices like watches [38], patches [39], rings [35], and contact lenses [29]. This integration enables the convenient application of electrochemical in vivo detection in everyday life, providing continuous, non-invasive health monitoring with significant clinical implications and vast potential for broad applications (Figure 1a).

Despite these advancements, critical gaps persist in systematic analyses of IVEB development trajectories and translational roadblocks. Existing reviews predominantly adopt narrow scopes, focusing on specific sensor architectures or analyte classes, while overlooking holistic assessments of clinical validation challenges and scalability constraints. To bridge this critical knowledge gap, we provide an extensive overview of the latest developments in IVEBs and discuss the existing shortcomings and future directions in this field. We also explore the prospects of employing artificial intelligence algorithms to optimize data processing workflows [40,41], which is expected to further advance personalized medicine and telemedicine. We hope to offer a comprehensive reference for researchers and developers in the field, helping them understand the current state of IVEBs, the challenges faced, and potential future solutions.

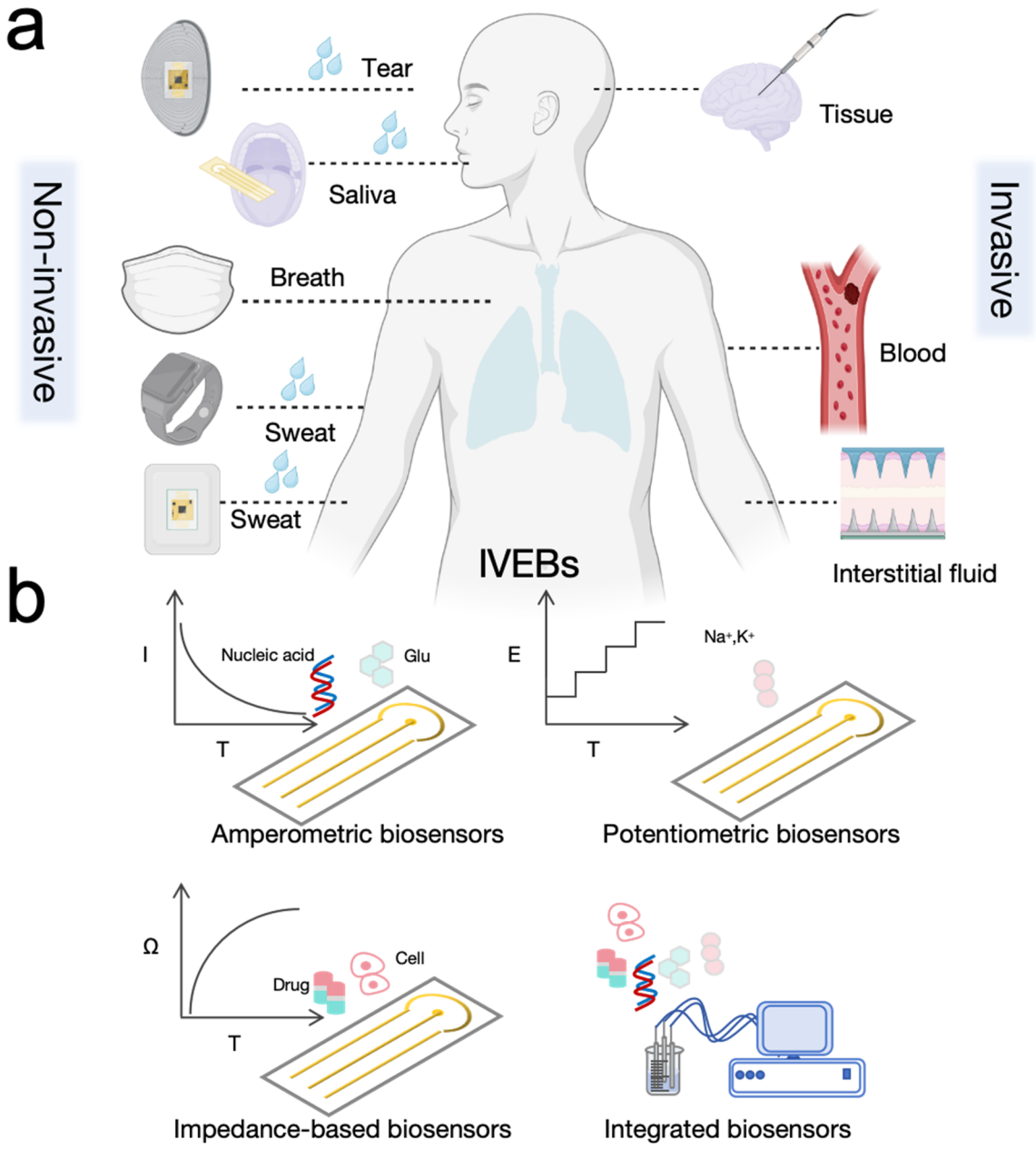

Figure 1. Schematic diagram of in vivo electrochemical sensor application. (**a**) In vivo detection applications. (**b**)In vivo electrochemical biosensors (Created with BioRender.com).

2. Diversification of IVEBs

IVEBs are of great importance in medical diagnostics and disease monitoring due to their ability to monitor biochemical reactions within the body in real-time. Among them, IVEBs have significant advantages over other in vivo biosensors in terms of detection accuracy and response speed due to their high sensitivity and selectivity. Currently, in vivo electrochemical biosensors can be mainly categorized into potentiometric biosensors, amperometric biosensors, impedimetric biosensors, and integrated biosensors (Table 1, Figure 1b).

Table 1. Different types of electrochemical biosensors.

Biosensor Type	Target	Materials	Advantages/Disadvantages	References
Potentiometric	Ions, pH, specific biomolecules	Au, carbon-based compounds, carbon (nano) materials	High selectivity for specific ions or molecules, has a longer response time compared to amperometric biosensors	[42]
Amperometric	Glucose, nucleic acid, ions	Pt, Au, Glassy Carbon	Highly sensitive and fast-responding, it can be influenced by environmental factors.	[18,43]
Impedance-based	Cell membranes and tissues	Au, Pt, carbon-based materials	Suitable for detecting complex biological systems without damaging the samples, high sensitivity, high cost, signal interference	[20]
Integrated	Various biomarkers	Au, Pt, carbon (nano) materials	Combining different sensors enhances detection accuracy for complex samples but may raise device cost and maintenance challenges	[44]

2.1. Potentiometric Biosensors

Potentiometric biosensors operate by gauging the voltage differential between a reference electrode and a sensing electrode to detect the concentration of specific analytes. The reference electrode maintains a stable half-cell potential, whereas the potential of the indicator electrode varies according to the activity or concentration of the target analyte in the solution. The change in potential is logarithmically proportional to the concentration [21,45]. The design of potentiometric biosensors is relatively simple and stable in operation, making them particularly suitable for long-term monitoring [42]. By using selective electrode materials, they can achieve high selectivity for specific ions or molecules. They are suitable for detecting electrolyte concentrations or ion activities, but are not suitable for detecting rapidly changing reactions. Typically, they only measure potential changes at equilibrium, and their response time may be longer compared to amperometric biosensors.

2.2. Amperometric Biosensors

Amperometric biosensors function by applying a voltage between a reference electrode and a working electrode to trigger the electrochemical oxidation or reduction of the analyte. The consequent current is then used as a quantitative measure of the analyte concentration [21,45]. Leveraging biomolecular recognition techniques, such as electrodes modified with antibodies or nucleic acid probes, amperometric biosensors have been extensively employed for the high-sensitivity detection of viral infections [46] and cancer biomarkers [47]. Amperometric biosensors are highly sensitive to changes in current, allowing for detection of low levels of analytes. Due to the instantaneous nature of current changes, they typically exhibit rapid response times. These sensors are particularly suitable for applications requiring the detection of electron transfer reactions, such as glucose sensors [48]. They rely on electron transfer events (e.g., redox reactions) during the biorecognition process to generate detectable current changes. Additionally, they are sensitive to the electrochemical conditions of the environment, such as electrode materials [49] and the pH of the solution [50].

2.3. Impedance-Based Sensors

Impedance-based sensors operate by measuring the changes in impedance that occur due to electrochemical reactions, and are commonly utilized to investigate the properties of electrochemical interfaces [51]. The application of novel materials, such as graphene or conductive polymers, has enhanced the performance of impedance-based sensors and broadened their prospective applications, particularly in areas such as monitoring cell growth and detecting environmental toxins [52–55]. Impedance biosensors can simultaneously measure multiple parameters such as resistance, capacitance, and inductance, thereby providing rich electrochemical information. They can detect complex biological systems, such as cell membranes [53] and tissues [56], without damaging the samples. Since the detection signals are usually small, they have minimal impact on the samples,

making them suitable for continuous monitoring. However, the testing process is complex and typically requires more sophisticated instruments and data analysis methods. Additionally, they are sensitive to frequency changes, necessitating scanning over a wide frequency range to obtain comprehensive impedance spectra.

2.4. Integrated Biosensors

For complex samples, a single type of sensor may not provide complete information. By combining different types of sensors, it becomes easier to detect complex samples and obtain more comprehensive and accurate analytical results. Therefore, integrating them is highly necessary. With the advancement of technology, an increasing number of sensors are employing a combination of various electrochemical detection techniques to enhance their capabilities. For example, the high sensitivity and rapid response capabilities of amperometric biosensors can be integrated with the high selectivity of potentiometric biosensors, thereby maintaining high sensitivity while improving selectivity for specific target substances. Additionally, the rich electrochemical information provided by impedance biosensors allows the entire detection system to obtain more comprehensive analytical data during the detection process [57].

3. Application of IVEBs

Compared to traditional ex vivo methods, IVEBs offer significant advantages, including the ability to monitor dynamic changes within biological systems in real-time and provide a more accurate reflection of physiological states. This real-time monitoring is particularly crucial for capturing transient or subtle changes that might be overlooked in ex vivo analysis [58]. Additionally, IVEBs reduce the risk of sample degradation or alterations that might occur during ex vivo processing. The integrated application of IVEBs, especially in wearable devices [59], makes continuous health monitoring and early disease detection possible, enabling timely detection and response to changes in health status. These biosensors can continuously monitor biomarkers in blood, interstitial fluid, body fluids, and in vivo tissues, thereby providing a comprehensive assessment of an individual's health status. With the development of IVEBs, non-invasive, wearable sensors have become a reality, greatly facilitating users and improving quality of life [60–62]. For example, clinical studies have shown that wearable devices have important applications in diagnosis and monitoring in neurology and psychiatry [58,63]. In addition, these IVEBs have shown significant potential for applications in studying the role of biomolecules such as neurotransmitters and oxidative stress in health and disease. Taken together, IVEBs show great promise for improving the efficiency of clinical diagnosis, advancing personalised medicine, and improving patient monitoring (Table 2). This review will further discuss the applications and advancements of invasive and non-invasive IVEBs.

3.1. Invasive IVEBs

Invasive IVEBs involve inserting electrodes directly into biological tissue to measure specific analytes. This method has the advantages of high accuracy [64] and real-time data**.** Currently, invasive methods primarily detect samples of blood, interstitial fluid, and tissue.

3.1.1. Blood Detection

Blood is a frequently utilized sample for diagnostic testing due to its rich repository of biomarker information, which can provide critical insights into various physiological and pathological conditions. Regiart et al. developed a highly sensitive and selective nanostructured microbiosensor designed for the simultaneous detection of glucose and lactate in both blood serum and brain tissue. This innovative sensor leverages carbon fiber microelectrodes modified with nanoporous gold, which significantly enhances sensitivity and selectivity through the incorporation of platinum nanoparticles and enzyme immobilization. These modifications allow for precise in vivo measurements of glucose and lactate concentrations in different brain regions, thereby offering valuable data on brain metabolism under various conditions [65] (Figure 2a). Zou et al. advanced the field by creating an electrochemical fiber sensor capable of real-time monitoring of homovanillic acid (HVA) in blood. This sensor utilizes a molecularly imprinted polymer recognition mechanism, which affords it exceptional accuracy—up to 97.8% in vivo. The ability to monitor HVA, a crucial metabolite, in real-time underscores the sensor's potential as a powerful tool for assessing key metabolic processes, thereby providing a significant advancement in biomedical research and clinical diagnostics [31] (Figure 2b).

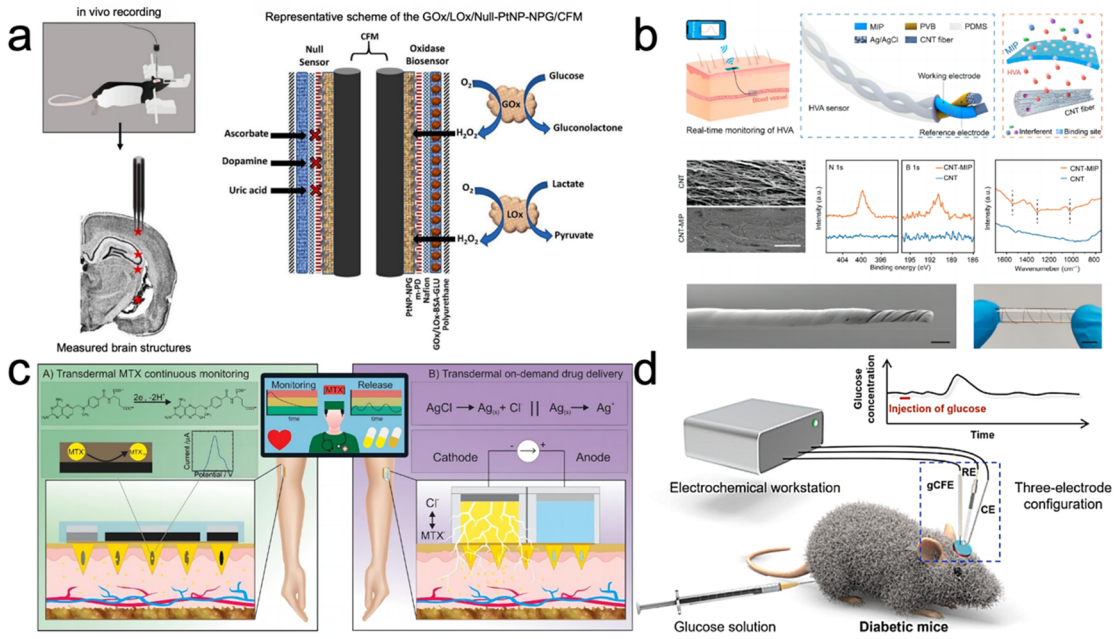

Figure 2. Invasive in vivo monitoring biosensing devices. (**a**) A biosensor for simultaneous measurement of glucose and lactate in serum and brain tissue [65]. Copyright 2022, Elsevier. (**b**) Schematic illustration and structural characterization of a highly selective implantable electrochemical Homovanillic acid (HVA) fiber sensor [31]. Copyright 2024, American Chemical Society. (**c**) A wearable microneedle array patch designed for ongoing electrochemical monitoring and methotrexate (MTX) administration [32]. Copyright 2023, American Chemical Society. (**d**) A carbon fiber microelectrode (CFE) implanted and modified with an osmium-derivatized polymer and glucose oxidase (GOx), referred to as gCFE, was developed as an effective instrument for in situ and real-time glucose measurement in the brains of mice [33]. Copyright 2023, American Chemical Society.

3.1.2. Interstitial Fluid Detection

Interstitial fluid is in direct contact with extracellular fluid and can reflect changes in the intercellular environment [66]. The application of IVEBs in interstitial fluids is often used to monitor important ions and metabolites such as glucose, potassium ions, sodium ions, etc. [67,68]. For example, Kotanen et al. studied the application of implantable enzyme amperometric biosensors in continuously measuring lactate levels in interstitial fluid, with a particular emphasis on the differences in lactate levels between interstitial fluid and blood in a traumatic shock model. This provides critical data for researching the temporal dynamics of stress biomarkers [43]. Parrilla et al. developed an in vivo sensor based on a hollow microneedle array, integrating microfluidic channels and an external injector, to achieve rapid interstitial fluid extraction. This method allows for continuous glucose monitoring. However, their study focused on glucose monitoring and lacks the capability to monitor and manage other biomarkers or drugs, limiting its potential in broader medical applications [69]. In 2023, the application of microneedle technology was improved and expanded on this basis; it not only includes monitoring functions but also drug delivery, specifically for methotrexate treatment [32] (Figure 2c). This multifunctional device facilitates a closed-loop system for ongoing monitoring and as-needed medication administration, resulting in a more thorough and effective health surveillance and management system. Yang et al. designed a in vivo microneedle biosensor integrating tetrahedral DNA nanostructures (TDN) and Natronobacterium gregoryi Argonaute (NgAgo) on a in vivo microneedle biosensor for real-time and sensitive monitoring of ultra-trace DNA and RNA in vivo [37]. Provides a new avenue for in vivo, continuous, and real-time monitoring of important health biomarkers.

3.1.3. Tissue Detection

By detecting specific biomarkers in tissues, it is possible to achieve early detection and diagnosis of various diseases, such as cancer, diabetes, and neurodegenerative diseases. Zhu et al. studied the application of IVEBs for glucose measurement in the brain and validated their practicality in diabetes management [33] (Figure 2d). Additionally, the microelectrode sensor developed by Monteiro et al. is capable of simultaneously measuring glucose and lactate in brain tissue, demonstrating its potential for detecting metabolic biomarkers in different brain regions, with significant implications for biomedical research [70]. Zhou et al. introduced an implantable electrochemical microsensor designed for real-time monitoring of oxygen levels in tissues, showing substantial

potential for applications in neuroscience research [52]. These studies highlight the critical role of microsensor technology in real-time in vivo monitoring and its broad prospects in biomedical research.

3.2. Non-Invasive IVEBs

Invasive IVEBs offer the advantages of high accuracy and real-time data but carry risks of tissue damage and infection. In contrast, non-invasive IVEBs measure analytes through the skin or other external tissues, reducing the risk of infection and eliminating tissue damage, making it safer and less painful for patients [71]. Non-invasive IVEBs are primarily applied in the detection of sweat, saliva, tears, and breath, to monitor substances such as glucose, drugs, and nucleic acids.

3.2.1. Sweat Detection

Sweat is a collectible biological fluid produced by highly vascularized sweat glands from plasma and interstitial fluid. It contains a wide array of biomarkers ranging from electrolytes and metabolites to hormones, neuro-markers, and drugs. Moreover, the continuous production of sweat allows for real-time health monitoring [30,72,73].

Detection of Glucose

Glucose is essential for cellular energy, but prolonged high levels can cause health issues like heart disease, nerve damage, and foot ulcers. Effective diabetes management is crucial [52]. Traditionally, blood glucose monitoring has relied on portable glucometers, which require multiple finger pricks daily, causing discomfort and pain [15,22,74–76]. To address this issue, researchers are developing non-invasive continuous glucose monitoring devices [15,77]. For example, an IVEB integrated into a wristband can monitor sweat glucose in real-time during physical exercise and transmit the data to a mobile app through Bluetooth [34] (Figure 3a). Sweat glucose sensors are continuously evolving, from monitoring exercise-induced sweat to inducing sweat production using an iontophoretic interface with a programmable current source, which also avoids electrode corrosion and skin discomfort [27,78] (Figure 3b). Additionally, researchers have developed a method for continuous monitoring of sweat glucose using machine learning algorithms, as well as an electrochemical in vivo sweat biosensor based on ultra-low volume membranes with a detection limit (LOD) of 0.01 mM and a minimum volume of 0.15 μL [40,79] (Figure 3c). These innovations in non-invasive glucose monitoring technology can improve the quality of life for diabetic patients by reducing discomfort and facilitating continuous health tracking.

Detection of Lactic Acid

Lactic acid is produced during anaerobic glycolysis when the body is engaged in high-intensity exercise and oxygen is in short supply [80]. It serves as an important biomarker for assessing muscle function and the body's physiological response to exercise. Saha et al. has proposed a non-invasive, wearable sweat sampling patch that uses osmosis and evaporation to collect sweat, enabling long-term lactate monitoring and providing insights into human metabolic activity [81]. Zhou et al. proposed an innovative wireless electrochemical in vivo sensing platform that utilizes osmotic sweat extraction and microfluidic technology for real-time continuous monitoring of lactate levels in sweat [82] (Figure 3d), which expanded the range of biomarkers for IVEBs.

Detection of Drug

Sweat IVEBs can detect biomarkers in the body as well as substances such as drugs [83]. Demonstrating high sensitivity and specificity for in vivo monitoring, Zhang et al. engineered a wearable electrochemical sensor based on an aptamer array (Apt1, Apt2, Apt1 + 2). This platform achieved ultrasensitive detection (e.g., LOD of 0.18 nM for cathinone) and successfully discriminated multiple psychoactive drugs (including cathinone, cocaine, heroin) in sweat samples collected from human subjects, showcasing its potential for non-invasive, real-time drug screening [84] (Figure 4a), providing new methods for drug monitoring in on-site and routine testing. This advancement holds significant promise for enhancing drug monitoring capabilities in various settings. A team has developed a wearable electrochemical sensing array for monitoring multiple anticancer drugs in sweat. It comprises three working electrodes modified with specific aptamers and has demonstrated 100% accuracy in identifying and distinguishing nine anticancer drugs in artificial sweat samples. This innovation offers a new method for real-time monitoring and precise adjustment of drug dosages in clinical practice [85].

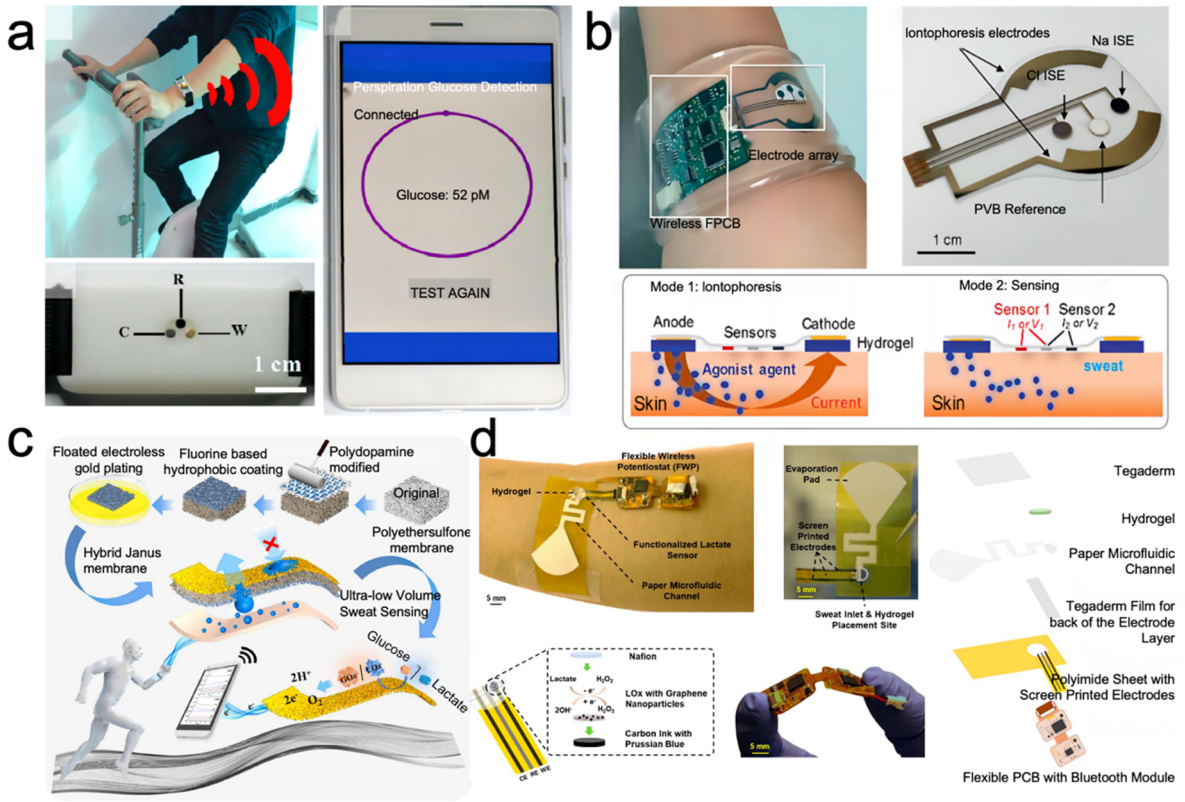

Figure 3. Advances in wireless sweat analysis via wearable electrochemical platforms. (**a**) A wrist-worn electrochemical sensor system for analyzing glucose levels in sweat during exercise [34]. Copyright 2018, American Chemical Society. (**b**) A wearable sensor designed for sweat analysis, capable of detecting glucose and ions, comprises an array of electrodes for both sweat and ion sensing [78]. Copyright 2016, American Chemical Society. (**c**) Diagram of the HJM showcasing dual-asymmetry integration of wettability and conductivity for wearable electrochemical sweat analysis [79]. Copyright 2022, American Chemical Society. (**d**) A wireless wearable electrochemical sensing platform for lactate monitoring [82]. Copyright 2022, American Chemical Society.

Multiplex Biomarker Detection

By detecting multiple biomarkers, doctors can obtain more comprehensive biological information, enabling early diagnosis and monitoring of diseases, as well as the formulation of personalized treatment plans to improve therapeutic outcomes [86,87]. Additionally, the combined analysis of multiple biomarkers can cross-validate, reducing the occurrence of false positives and false negatives, leading to more accurate diagnosis [88,89]. For example, Shahub et al. and Wang et al. pioneered multiplexed electrochemical sensing platforms capable of simultaneous, noninvasive detection of trace-level metabolites (e.g., amino acids, vitamins) and protein biomarkers (e.g., GFAP, IL-6) in passively expressed sweat, enabling continuous monitoring of nutritional status and neurological injury [38,73] (Figure 4b). Sanghyuk Yoon et al. also integrated electrocardiogram (ECG) functionality [39], while Wanget al. developed an ultra-miniature in vivo biosensor system integrated into a single MS02 chip measuring only 1.2 mm × 1.1 mm, significantly reducing its size and enabling real-time, multi-channel, high-precision sweat analysis [90] (Figure 4c). This collective advancement in IVEBs highlights the growing importance and feasibility of multi-biomarker detection for more precise and personalized healthcare applications.

3.2.2. Tear Fluid Detection

Tears contain a variety of biomarker molecules and are exposed for easy collection [29,91]. In addition, tear composition is positively correlated with blood levels due to the blood-tear barrier, demonstrating the feasibility of monitoring tears as a biomarker of disease [29,92,93]. Song et al. engineered a wireless, soft smart contact lens platform incorporating an electrochemical biosensor, a stretchable antenna, and integrated circuits. This device facilitates non-invasive, real-time quantitative monitoring of free cholesterol levels in tear fluids for diagnostic assessment of hyperlipidemia, operated solely via smartphone [29] (Figure 5a). Park et al. developed a smart contact lens capable of continuously monitoring glucose levels in tear fluid and wirelessly transmitting the data to

a smartphone. The study validated a close correlation between glucose levels in tear fluid and blood glucose levels, indicating the potential of this device as a non-invasive blood glucose monitoring tool for diabetic patients [94] (Figure 5b). These advancements in smart contact IVEBs highlight the growing potential of non-invasive, real-time monitoring systems for managing chronic diseases through the analysis of tear fluid biomarkers.

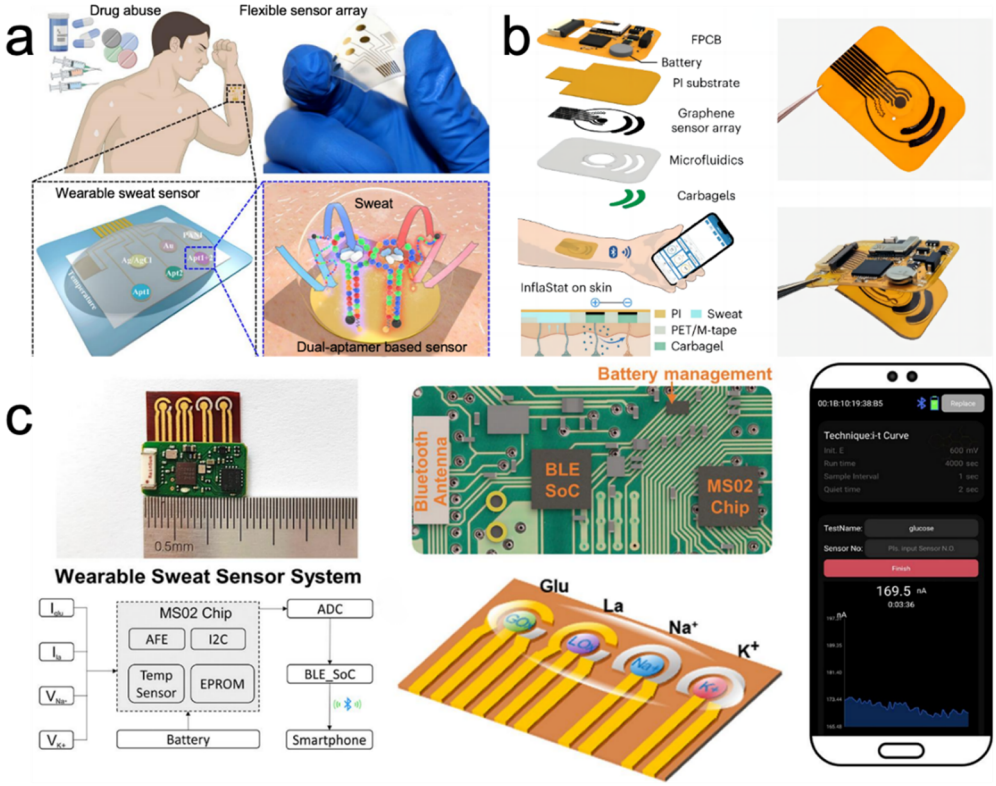

Figure 4. Integrated wearable sweat sensors for real-time monitoring of drugs and metabolites. (**a**) A wearable system designed for the detection and monitoring of psychoactive substances [84] Copyright 2022, American Chemical Society. (**b**) A sensing platform capable of simultaneously detecting trace amounts of multiple metabolites and nutrients in sweat [38] Copyright 2022, American Chemical Society. (**c**) A miniature in vivo biosensor system integrated into a single MS02 chip with dimensions of only 1.2 mm × 1.1 mm [90] Copyright 2022, American Chemical Society.

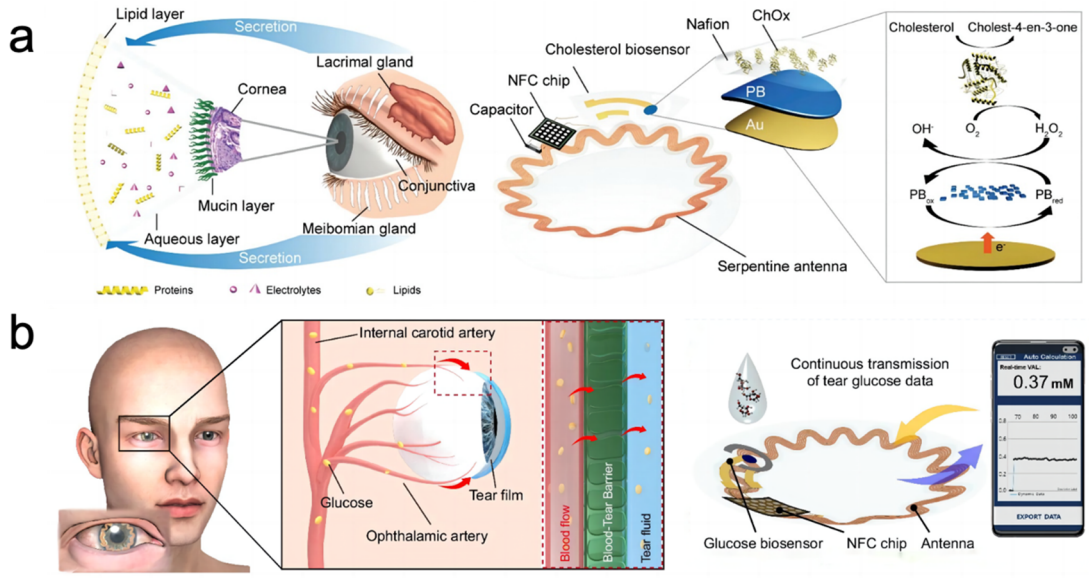

Figure 5. In vivo tear electrochemical biosensor. (**a**) Point-of-Care tear cholesterol monitoring via smart contact lens [29]. Copyright 2022, American Chemical Society. (**b**) Smart Contact Lens for Tear Glucose Detection [94]. Copyright 2024, American Chemical Society.

3.2.3. Saliva Detection

Saliva, due to its ease of collection and ability to reflect blood components, is considered a potential alternative to blood analysis. In recent years, saliva analysis has garnered interest for its non-invasive and convenient potential as a substitute for conventional diagnostic and monitoring methods, capable of providing a wealth of personal health information [95–97]. A research team has developed a wearable salivary uric acid detection mouthguard biosensor integrated with wireless electronics. This device is capable of real-time and continuous monitoring of uric acid levels in saliva and can be expanded to detect other analytes, offering a new platform for diverse health and biomedical daily applications [98] (Figure 6a). For immediate detection of drunk driving and drug use, saliva is an excellent substrate. Mishra et al. developed a wearable electrochemical ring sensor integrating a miniaturized wireless electronic board within the ring body and a replaceable, screen-printed dual-sensor cap for the simultaneous, on-site detection of salivary Δ^9-tetrahydrocannabinol (THC) and alcohol [35] (Figure 6b). While the platform can be effective in addressing public safety issues. However, Saliva samples need dilution for effective analysis, which may affect the feasibility of on-the-spot testing. Furthermore, a recent study introduced a smart bioelectronic pacifier capable of real-time, continuous, and non-invasive monitoring of sodium and potassium levels in neonatal saliva. This flexible and miniaturized system integrates ion-selective electrodes and microfluidic channels directly into a commercial pacifier, providing a comfortable and clinically feasible solution particularly suited for neonatal care. The device not only overcomes the challenges of discrete sampling and rigid structures but also further expands the clinical utility of saliva-based biosensing technologies [99] (Figure 6c).

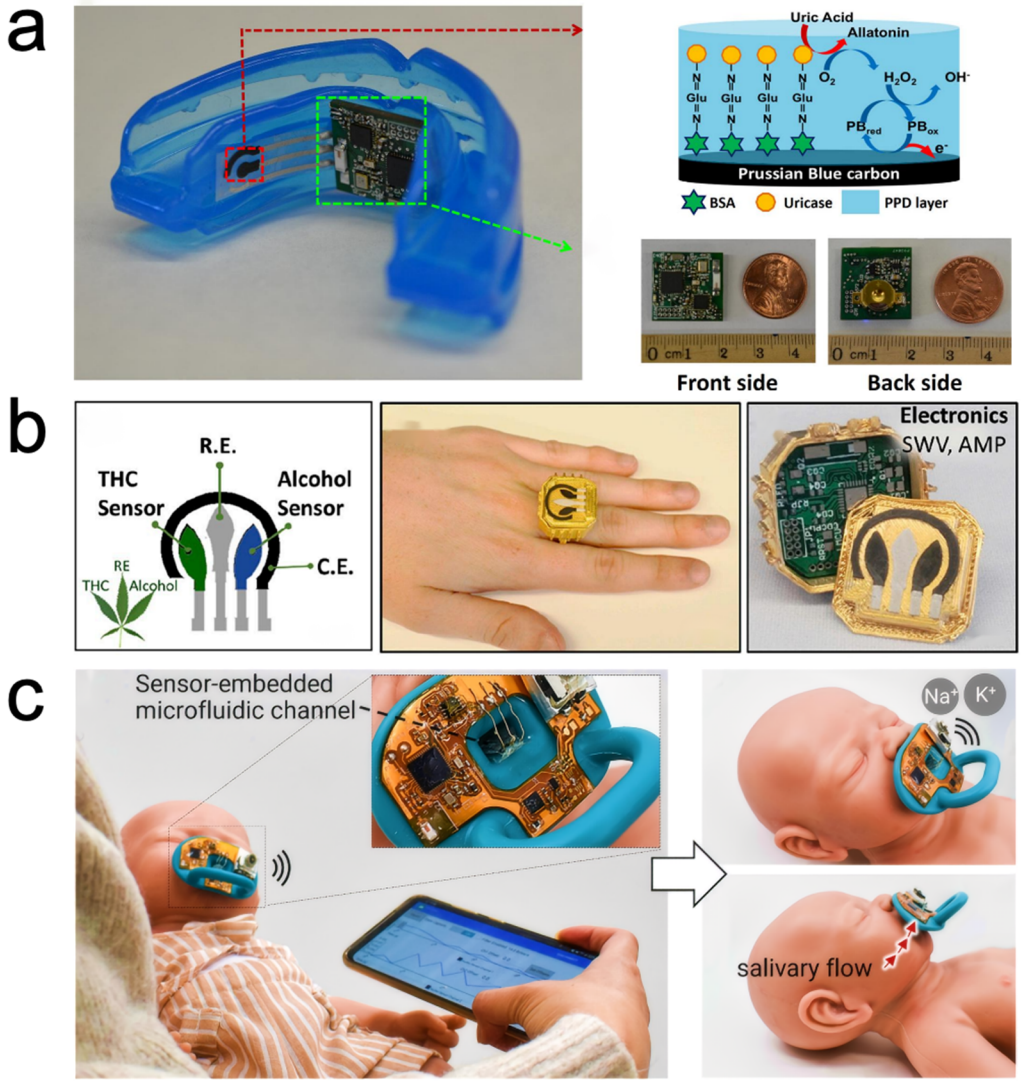

Figure 6. In vivo saliva electrochemical biosensor. (**a**) Wearable mouthguard sensor for salivary uric acid detection [35]. Copyright 2020, Elsevier. (**b**) Wearable ring sensor for alcohol and drug detection [98]. Copyright 2015, Elsevier. (**c**) Smart bioelectronic pacifier [99]. Copyright 2022, Elsevier.

3.2.4. Breathing Detection

Respiratory monitoring often requires complex, expensive, and bulky equipment, which greatly limits its medical applications. Jin et al. designed a fully integrated in vivo humidity sensor for respiratory monitoring, a device designed to monitor respiration through humidity detection. It consists of flexible lcp-copper interdigital electrodes, a sensing layer, and a radiochemical analysing system, highlighting the advances in in vivo sensor technology [100] (Figure 7a). Choi et al. developed a flexible humidity sensor by integrating ultra-small platinum nanoparticles (≈2 nm) onto nitrogen-doped reduced graphene oxide (nRGO) fibers, achieving high sensitivity (4.51%@66.4% RH) and a broad detection range (6.1–66.4% RH); the Pt-catalyzed water dissociation mechanism significantly accelerated response dynamics. This sensor enables real-time monitoring of human exhaled breath humidity, providing a novel high-integration and low-power sensing strategy for wearable electrochemical in vivo detection systems [101] (Figure 7b). Xue et al. developed a highly sensitive near-field electrochemical sensor that utilizes electrochemical impedance and graphdiyne oxide (GDYO) for wireless coupling, demonstrating high sensitivity under low humidity conditions, making it suitable for respiratory pattern monitoring in biomedical research [36]. Furthermore, Wang et al. developed a wearable respiration sensor based on CeO_2@PANI nanocomposites for real-time detection of ammonia (NH_3) in the exhaled breath of patients with chronic kidney disease. The sensor demonstrated excellent repeatability, selectivity, and long-term stability, enabling differentiation between patients with varying stages of kidney disease and healthy individuals, thereby highlighting its potential for clinical disease monitoring [102] (Figure 7c).

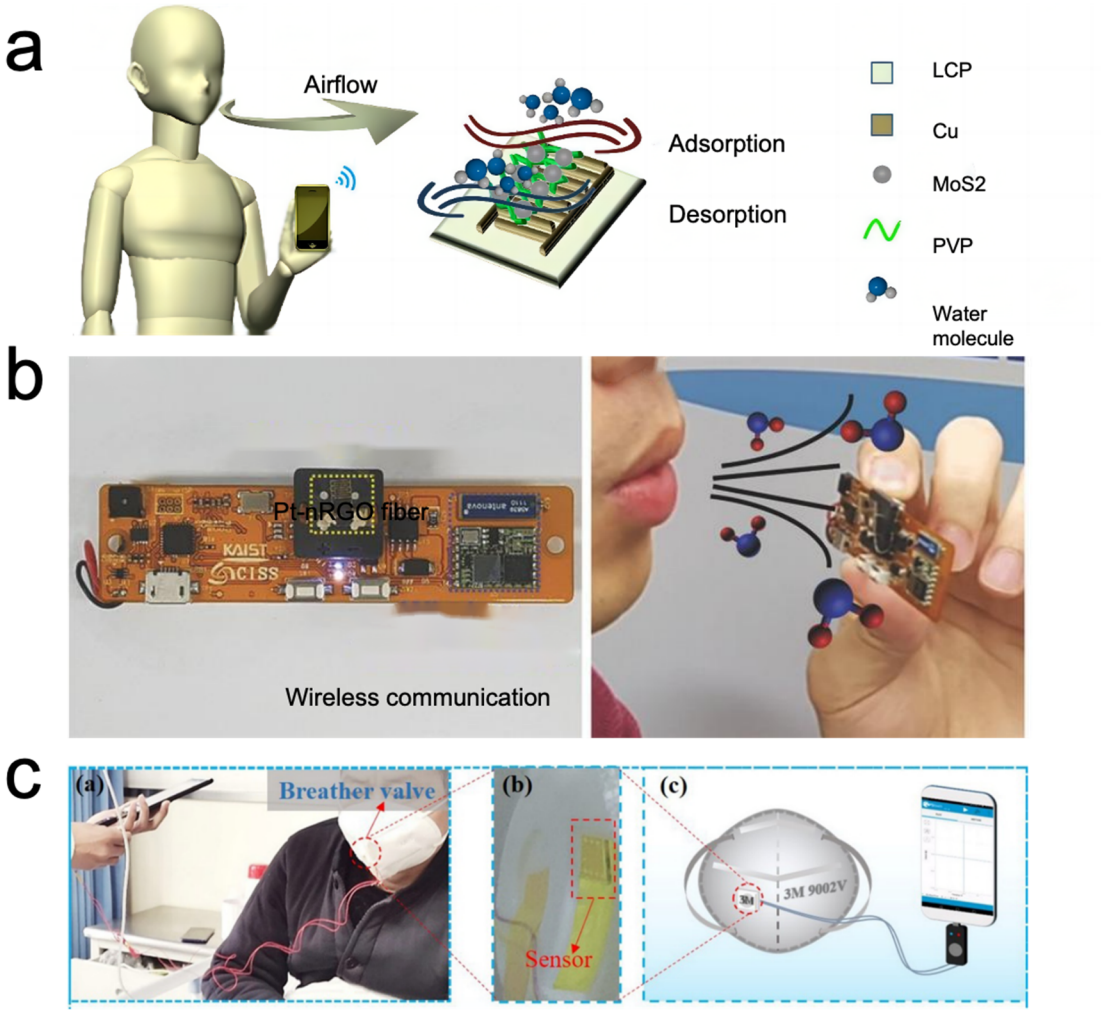

Figure 7. In vivo breath electrochemical biosensor. (**a**) fully integrated implantable humidity sensor for respiration monitoring [100]. Copyright 2022, Jin, Zha, Wang, Wang and Zhang. (**b**) Fully integrated implantable humidity sensor for respiration monitoring [101]. Copyright 2018, Wiley. (**c**) Wearable respiratory sensor for real-time monitoring of chronic kidney disease [102]. Copyright 2022 American Chemical Society.

Table 2. The specimens and substances for IVEBs.

Sample	Target	Reference
Blood	Glucose, Lactate, Hva	[31]
Interstitial fluid	Glucose, Lactate, Drug, RNA, DNA	[37]
Tissue	Glucose, Lactate, Oxygen	[33,52,70]
Sweat	Glucose, Lactate, Drug	[34,78,79,81]
Tear	Glucose, Cholesterol	[29,94]
Saliva	Uric acid, THC, Alcohol	[35,98]
Breath	Humidity, Oxygen	[36]

4. Conclusions

In this review, we comprehensively explore the principles and significant advantages of IVEBs, with a particular emphasis on their critical applications in the field of non-invasive health monitoring. With advancements in microelectronics technology, IVEBs have achieved miniaturization and portability, driving the use of portable devices for routine health monitoring among patients with chronic diseases such as diabetes. IVEBs offer significant advantages, such as highly sensitive real-time monitoring, non-invasive detection methods, and seamless integration with modern electronics and intelligent medical systems. These benefits position them as a promising yet challenging area in healthcare technology. Integrating IVEBs into wearable devices represents a major leap towards non-invasive, real-time, and continuous health monitoring, especially for managing chronic diseases.

Despite significant advancements, current IVEBs face several key challenges. Detecting low-concentration biomolecules like cortisol and insulin with high sensitivity and accuracy remains difficult. IVEBs should maintain high specificity for diverse biomarkers, minimizing interference from other substances in bodily fluids, ensuring consistent accuracy across various populations and environmental conditions. Emerging samples like sweat and tears pose challenges due to limited volumes and numerous interfering substances, leading to result instability. Therefore, developing novel nanomaterials, biocompatible materials, and biomolecular recognition elements to enhance IVEBs sensitivity and selectivity is necessary. Integrating IVEBs systems with functionalities such as data transmission and drug delivery into small, portable, and durable sensors is challenging. Ensuring these sensors remain comfortable to wear without compromising performance is a significant hurdle. Additionally, addressing energy supply and signal processing issues is critical for the long-term stable operation of these sensing systems. Advancements in non-invasive and minimally invasive technologies will improve the multi-component integration degree and increase user comfort. IVEBs' performance varies with the composition of bodily fluids and individual differences, necessitating tailored sensor designs for different individuals. Current IVEBs primarily detect single analytes like glucose. Expanding their capability to simultaneously detect multiple biomarkers is essential for future development. Artificial intelligence and cloud computing integration will facilitate real-time analysis and personalized health management.

The clinical translation of IVEBs entails a multifaceted challenge, encompassing regulatory compliance, cost-efficiency, and biocompatibility. Regulatory frameworks must evolve to accommodate the rapid technological progress of IVEBs while ensuring their safety, efficacy, and interoperability within healthcare systems. Compliance with standards such as ISO 10993 for biocompatibility and IEC 60601 for electrical safety is critical, as is rigorous clinical validation across diverse patient populations. Equally important is the economic viability of these devices; affordability hinges on scalable manufacturing processes, material selection, system maintenance, and potential reimbursement policies. Strategies such as utilizing low-cost and biocompatible materials (e.g., PDMS, polyimide, hydrogels) and adopting microfabrication or printing-based approaches can significantly lower production costs without compromising performance.

Biocompatibility remains a cornerstone for long-term sensor functionality in vivo. As highlighted in recent studies, the selection of bioinert and mechanically compliant materials, along with anti-fouling strategies, is vital to mitigate immune responses and maintain signal stability during continuous monitoring. For instance, integrating nanostructured electrodes with hydrogels or flexible substrates can enhance bioreceptor immobilization and device-tissue conformity, thereby improving analytical performance and wearer comfort.

Beyond engineering challenges, ethical and societal dimensions are equally essential. Continuous physiological monitoring via IVEBs generates high-resolution personal data, necessitating strict data governance frameworks to protect privacy, ensure informed consent, and prevent potential misuse, including unauthorized surveillance. Adherence to data protection regulations (e.g., GDPR, HIPAA [103]) and transparent algorithmic processes are indispensable in fostering public trust. Moreover, user-centered design is critical for sustained engagement. Devices must be ergonomic, intuitive, and minimally invasive to accommodate daily use. Close collaboration among engineers, clinicians, designers, and end-users is essential to ensure that IVEBs are not only

clinically effective but also human-centric in design, ultimately promoting widespread acceptance and equitable deployment.

Strengthening interdisciplinary collaboration will drive technological innovation, ensuring that IVEBs meet clinical needs. Continuous research and technological advancements are expected to transform personal health management, early disease diagnosis, and treatment, especially in chronic disease management and preventive medicine. Breakthroughs in IVEBs integration and full-function controllers and modules will expand the clinical applications, marking a significant leap towards non-invasive, real-time, and continuous health monitoring systems.

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