

REVIEW

Implantable electrochemical sensors for continuous blood monitoring

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Abstract

The dynamic changes in blood physicochemical properties are regarded as the most direct and immediate window into the physiological state of the body, which cannot be captured by conventional intermittent blood sampling and analysis. The emergence of implantable electrochemical sensors offers a transformative solution, enabling blood to be monitored directly, in situ, and continuously, thereby potentially shifting medical diagnosis from a standardized model based on population averages toward an era of dynamic, individualized analysis. Recent developments have focused on material design and sensing technologies, through which continuous monitoring of multiple key analytes in blood has been achieved. This review systematically examines this rapidly advancing field. The unique properties of blood and their influence on sensing strategies and device design requirements are analyzed. Subsequently, newly developed materials and advanced fabrication technologies that address these challenges are surveyed. Furthermore, recent progress in two key application scenarios, real-time intraoperative physicochemical monitoring and long-term pharmacokinetic studies, is highlighted. Finally, the core challenges for clinical translation are discussed, and future research directions are outlined, aiming to provide a clear roadmap for interdisciplinary collaboration and to accelerate the translation of this technology from the laboratory to the clinic.

KEYWORDS

blood monitoring, clinical translation, electrochemical sensor, implantable sensor, precision medicine

1 | INTRODUCTION

Blood, as the central conduit of the systemic circulation, serves as the carrier of overall physiological and pathological information. Changes in its physicochemical properties

are direct and immediate reflections of physiological regulation and pathological processes.^{1,2} Modern medicine has established a comprehensive diagnostic system based on blood indicators. For instance, blood glucose is the undisputed gold standard for diagnosing and managing

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diabetes.³ Critical care and major surgeries rely on the precise tracking of blood electrolytes (K^+ , Ca^{2+}) and gases (pH, pO_2) as fundamental vital signs.⁴ In pharmacology, therapeutic drug monitoring via plasma concentration is essential for dosing potent medications with narrow therapeutic windows, such as antibiotics,⁵ anticoagulants,⁶ and chemotherapeutics.^{7,8} Furthermore, blood harbors pivotal biomarkers⁹ for conditions ranging from heart failure (troponin¹⁰) to cancer (circulating tumor DNA¹¹).

All of these achievements are founded on a paradigm of blood sampling, followed by centralized laboratory analysis. The paradigm offers high accuracy, established standardization, and the ability to simultaneously analyze a broad panel of biomarkers, remaining the gold standard for diagnostic confirmation. However, it suffers from inherent limitations of intermittence, accompanied by critical blind spots and delays. It misses rapid physiological transitions (e.g., sudden hyperkalemia¹²), and fails to capture the rich, dynamic patterns inherent in human physiology, which are essential for precision medicine. Furthermore, since the volume of blood collected is minimal compared to the total blood volume in the human body, sampling bias may occur for trace circulating biomarkers.¹³ Specifically, insufficient sample volume may lead to ineffective capture of the target biomarkers, thereby introducing analytical errors and ultimately affecting the diagnostic results.

To overcome these constraints, implantable electrochemical sensors have been developed,^{14,15} which enable direct and continuous access to the bloodstream (Figure 1). By residing within the blood vessels, the sensors capture transient physiological events and rich dynamic chemical information through electrochemical transduction, essential for precision medicine, while eliminating sampling bias. Rather than replacing conventional blood testing, implantable sensors are poised to complement it by addressing gaps that conventional methods cannot fill. Significant progress has been made in recent years. Researchers have demonstrated two primary implantable device paradigms: Standalone sensors for intravascular implantation and sensors integrated with existing intravascular medical devices (e.g., venous catheters). Continuous monitoring of diverse chemical species in blood has thus been achieved, from critical biomarkers to therapeutic drugs in animal models.

It is thus necessary while remains unavailable to comprehensively review this exciting field of implantable electrochemical sensors for continuous blood monitoring. In this review, we first analyze how the unique properties of blood shape sensing strategies and design requirements. We then review the recent progress of new materials and fabrication technologies for the generation of these blood sensors, and highlight their applications in real-time intra-

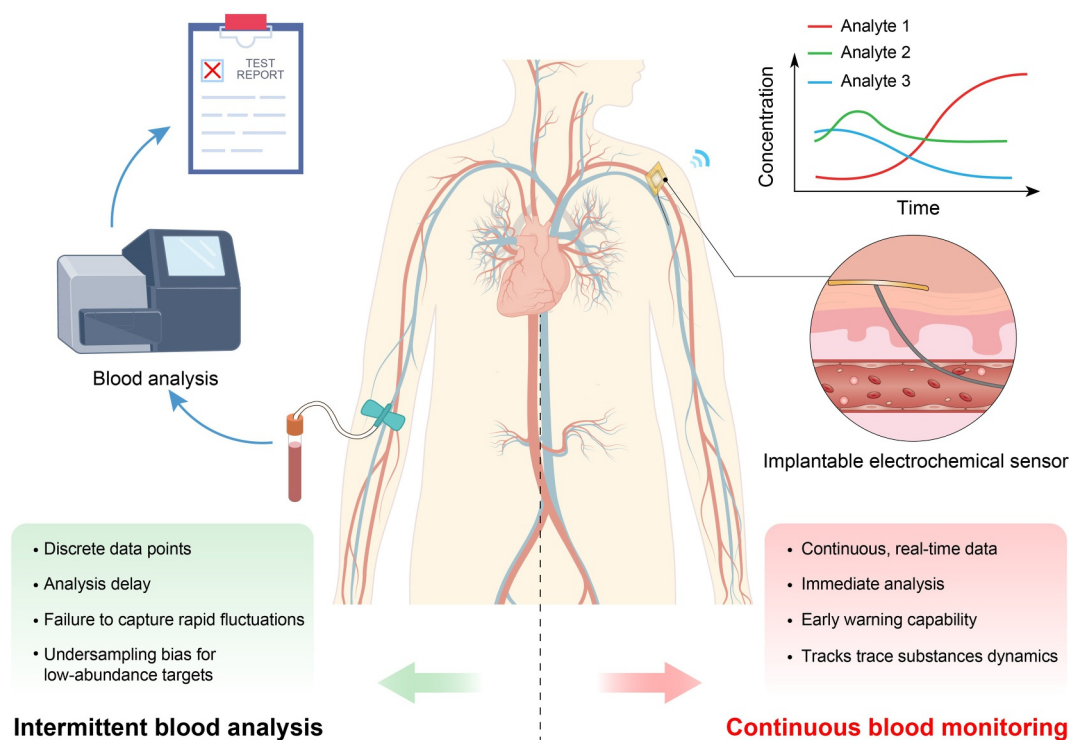


FIGURE 1 Schematic illustration of conventional intermittent blood sampling and continuous blood monitoring using implantable electrochemical sensors.

operative surveillance and drug metabolism monitoring. Finally, we discuss the outstanding challenges for clinical translation and outline promising directions. By systematically outlining recent advances and highlighting future directions, we seek to illuminate the pathway toward clinical translation and call for collaborative efforts across relevant disciplines.

2 | PRINCIPLES FOR ELECTROCHEMICAL SENSING IN BLOOD

Successful electrochemical sensing in blood hinges on a fundamental understanding of its unique physicochemical environment. Consequently, in this section, we first analyze the unique electrochemical properties of blood as an electrolyte. Building on this foundation, we then discuss sensing mechanisms specifically adapted to this medium, and finally establish a set of performance metrics for evaluating electrochemical sensors designed for blood monitoring.

2.1 | Blood: The unique electrochemical environment

For implantable electrochemical sensors, blood presents a uniquely challenging environment that extends far beyond its role as a mere electrolyte. It is a dynamic, complex, and highly reactive physiological system whose chemical composition, biological responses, and physical properties collectively impose fundamental constraints on sensor design and sensing performance.

2.1.1 | Direct interference from the chemical environment

As an aqueous electrolyte containing approximately 91 wt% water, blood maintains a high ionic strength typically ranging from 140 to 160 mM,¹⁶ dominated by Na^+ , Cl^- , K^+ , Ca^{2+} , etc. The higher ionic strength compresses the thickness of the double layer (the thickness of the double layer is inversely proportional to the square root of the ionic strength). Consequently, the available potential window for sensing becomes constrained, and even minor potential variations induce substantial non-Faradaic capacitive currents that can significantly mask the signal.

Meanwhile, the blood contains abundant endogenous electroactive substances, such as ascorbic acid (40–100 μM),¹⁷ uric acid (150–450 μM),¹⁸ catecholamines,

etc. These molecules react under relatively low oxidation potentials (typically $< +0.6$ V vs. Ag/AgCl),^{19,20} generating considerable background Faradaic currents at specific voltages and thereby interfering with target detection.

2.1.2 | Biofouling and interface passivation

In addition to small molecules, the blood also contains large protein molecules (~ 7 wt%) such as albumin, fibrinogen, and γ -globulin, as well as numerous non-adherent cells, including red blood cells ($4.2\text{--}6.2 \times 10^6 \text{ mL}^{-1}$), white blood cells ($4.5\text{--}11 \times 10^6 \text{ mL}^{-1}$), and platelets ($1.5\text{--}4.0 \times 10^6 \text{ mL}^{-1}$).²¹ The above components play a core role in triggering a series of biological reactions when foreign materials are exposed to the blood, which not only degrades the sensing performance but also raises significant biocompatibility concerns.²²

To be specific, the reaction starts with the rapid (milliseconds) non-specific adsorption of plasma proteins on the sensor surface,²³ forming a “protein halo.” This layer impedes the electron transfer kinetics and alters the interface properties, including dielectric constant, charge distribution, and hydrophobicity, leading to unpredictable drift in the double-layer capacitance and charge transfer resistance. The adsorbed proteins also represent the initial “foreign body” recognition by the host, which undergoes conformational remodeling to facilitate blood cell adhesion as well as activate coagulation and complement cascades.²⁴ As a result, a fibrin network intertwined with platelet emboli is formed, which captures red blood cells and white blood cells to gradually stabilize the thrombus. The resulting thrombus acts as a dense physical barrier, severely limiting analyte diffusion to the active surface and leading to rapid signal loss. The local thrombosis also poses risks of vessel occlusion and, if embolized, distal infarction.²⁵ It also initiates an acute inflammatory response,²⁶ damaging surrounding tissues.

If injuries are caused by sensor implantation, a chronic foreign-body response ensues. Macrophages recognize the sensor as a persistent insult and release inflammatory cytokines²⁷ (e.g., tumor necrosis factor- α , interleukin-6), followed by fibroblast activation and collagen deposition, forming an avascular fibrous capsule in the long term. This dense, stable capsule creates a persistent diffusion barrier, causing irreversible signal attenuation and functional failure. It also represents chronic inflammation, replacement of healthy tissue with scar tissue, and a risk of infection, all of which undermine the long-term safety and acceptance of the implant. Conclusively, the biological response to an implanted sensor follows a clear trajectory: from instant interfacial

fouling, to acute physical blockage, and finally to chronic fibrous isolation.

2.1.3 | Physicomechanical and geometric constraints

In addition to the chemical components of blood, we also need to consider the influence of the biophysics and mechanical properties of blood on electrochemical sensing. As a typical non-Newtonian fluid,²⁸ blood exhibits shear-dependent viscosity. This property becomes relevant in the context of varying blood flow velocities (ranging from 0 to 60 cm s⁻¹ in different vessels), where the uneven surface of an implanted sensor may create local low-shear zones. Consequently, local blood viscosity increases, leading to heterogeneous mass transport between different regions of the sensor surface, which in turn compromises signal uniformity and stability. Moreover, continuous blood flushing and shearing pose severe challenges to the adhesion of the active layer on the sensor, and it is necessary to avoid the detachment of the active layer that leads to signal attenuation.

Finally, blood flows through the blood vessels. Therefore, we also need to consider the requirements of the vessel size for the shape and size of the sensor. Vessels are one-dimensional tubular structures, and their sizes vary depending on the type of vessel.²⁸ The wall thickness/lumen diameter of the largest vena cava is typically 1.5/30 mm. For veins and venules, this figure is usually 0.5/5 mm and 30/30 μ m, while the lumen diameter of capillaries is even only 6 μ m. Therefore, the electrochemical sensors implanted in the blood vessels should be as small as possible to avoid damaging the vascular tissue and blocking the flow of blood in the vessels.

2.1.4 | Summary: Implications for sensor design

The above analysis reveals that the blood environment imposes multifaceted constraints and challenges on implantable electrochemical sensors, which collectively dictate several key design principles. First, to mitigate chemical interference, including high ionic strength and abundant endogenous electroactive species, sensing strategies must prioritize high selectivity, achieved through the use of specific recognition elements or detection methodologies that effectively discriminate target signals from background noise. Second, to address biofouling and the ensuing foreign-body response, the sensor interface

must incorporate antifouling strategies to resist protein adsorption, thrombosis, and fibrous encapsulation, thereby preserving signal fidelity and long-term biocompatibility. Third, the geometric and mechanical characteristics of the vasculature require sensors to be miniaturized and preferably flexible to accommodate the tubular structure of blood vessels, minimize hemodynamic disturbance, and maintain stable interfacial contact under dynamic physiological conditions. These design imperatives are not mutually exclusive but rather must be integrated synergistically. The following sections will elaborate on the materials and device architectures developed to meet these interconnected requirements.

2.2 | Sensing mechanisms adapted for blood monitoring

Based on the understanding of the electrochemical properties of blood, the electrochemical sensing mechanisms used for blood monitoring are discussed. According to the types of signals output, four of the most common sensing mechanisms are analyzed, including potentiometry, amperometry, voltammetry, and impedimetry, and their working principles and the limitations they face in blood monitoring are explained (Table 1).

2.2.1 | Potentiometry

Potentiometry quantifies analytes by measuring the equilibrium potential between a working electrode and a reference electrode under near-zero current flow,²⁹ namely an open-circuit condition. The measured potential conforms to the Nernst equation, meaning that the potential change is linearly related to the logarithm of the analyte concentration.³⁰ Two primary implementations are employed in blood monitoring. One is direct ion sensing based on ion-selective membranes modified on the working electrode,³¹ where target ions induce a membrane-potential shift. The other is indirect enzymatic sensing, which transduces local ion-concentration changes (e.g., H⁺) resulting from enzyme-catalyzed reactions into measurable signals.³² Potentiometry offers non-destructive detections, high temporal resolution (second-level), low power consumption, and relatively straightforward data interpretation. Nevertheless, the complex blood environment brings numerous factors contributing to potential fluctuations, including protein adsorption, hemodynamic variations, pH fluctuations, temperature shifts, and the hydration layer between the

TABLE 1 Comparison of electrochemical sensing mechanisms for blood monitoring.

Mechanism	Principle	Advantages	Limitations
Potentiometry	Measures equilibrium potential under near-zero current	1. Non-destructive 2. High temporal resolution 3. Low power consumption 4. Simple data interpretation	1. Drift-prone 2. Sensitive to environmental changes
Amperometry	Measures faradaic current from redox reaction at constant potential	1. Rapid response 2. Easy miniaturization 3. Simple instrumentation 4. Simple data interpretation	1. High background current 2. Susceptible to electroactive interferents 3. Analyte depletion
Voltammetry	Scans potential and records current-potential curves	1. Abundant kinetic information (CV) 2. High sensitivity (DPV) 3. Effective background subtraction (SWV)	1. Complex signal processing 2. Higher power consumption 3. Limited temporal resolution
Impedimetry	Applies a small AC potential perturbation and measures impedance response	1. Non-destructive 2. Rich interfacial information	1. Complex data interpretation 2. Sensitive to environmental changes 3. Limited temporal resolution

Abbreviations: CV, cyclic voltammetry; DPV, differential pulse voltammetry; SWV, square wave voltammetry.

ion-selective membrane³³ and the electrode, etc. Therefore, the accuracy and stability of the test results in the blood by potentiometry need to be carefully evaluated.

2.2.2 | Amperometry

The method of monitoring the Faraday current generated by oxidation or reduction reactions occurring on the working electrode surface under a constant potential, and thereby achieving quantitative measurement of the target analyte, is called amperometry. The change of current signal is thus proportional to the analyte concentration. The core advantage of amperometry lies in its rapid response speed and ease of miniaturized integration, requiring essentially only a potentiostat. However, its application in blood is significantly constrained by several factors. First, non-faradaic currents exert a pronounced influence. The high ionic strength of blood increases the double-layer capacitance; even minute fluctuations in electrode potential (caused by solution convection or ionic thermal motion) can generate substantial non-faradaic currents (μA), which can mask the much weaker faradaic signal. Furthermore, once the potential is applied, the redox reaction of the target molecule proceeds continuously at the electrode surface. Consequently, the current tends to decay as the analyte is depleted locally.³⁴ Finally, the presence of high concentrations of endogenous electroactive species in blood gives rise to a persistent background current under the operating potential, further interfering with the extraction of the specific target signal.

2.2.3 | Voltammetry

This method realizes the detection and analysis of target information by scanning the working potential and recording the current-potential curve. According to the different ways of scanning potential, voltammetry can be subdivided into various types. Cyclic voltammetry (CV) applies a cyclic triangular wave potential to the working electrode to measure the current response as a function of potential. Although CV offers only modest sensitivity and often requires slower scan rates to reveal detailed electrochemical features, it remains an exceptionally powerful tool for probing electrode reaction mechanisms.³⁵ Thus, it is particularly well-suited for preliminary investigations of interfacial processes between the electrode and electrolyte prior to formal analytical measurements.

Differential pulse voltammetry (DPV) applies a ramping baseline potential to the working electrode and superimposes a fixed-amplitude, short-duration potential pulse at each potential step. The current is measured immediately before (I_1) and shortly before the end (I_2) of each pulse, and the difference ($\Delta I = I_2 - I_1$) is recorded. The underlying principle relies on the distinct temporal responses of faradaic and non-faradaic currents: non-faradaic currents dominated by double-layer charging decay almost completely within milliseconds after the pulse is applied, whereas faradaic currents, governed by the diffusion and interfacial kinetics of the target molecules, evolve on a slower timescale.³⁶ By sampling the current difference across the pulse, the rapidly decaying non-faradaic contribution is effectively subtracted,

allowing the subtle faradaic signal of redox reactions to be clearly resolved. Consequently, DPV is exceptionally well-suited for detecting trace-level analytes.

Unlike DPV, square wave voltammetry (SWV) superimposes a symmetric square wave onto the ramping baseline potential. This waveform enables the simultaneous exploitation of both the symmetry and the rapid decay of capacitive currents in the forward and reverse potential halves, leading to even more effective background subtraction and thus higher sensitivity than differential-pulse methods. Furthermore, SWV offers the distinct advantages of rapid scanning³⁷ (yielding high temporal resolution) and the ability to extract multiple parameters (such as forward/reverse current components) from a single scan, providing richer kinetic information about the electrode process.

It is important to note that while voltammetry exhibits substantial advantages, its deployment in long-term, continuous blood monitoring imposes distinct engineering demands on the signal acquisition and processing pipeline. To ensure data consistency and comparability, standardized data processing protocols must be established. These include automated baseline correction, feature peak identification, and integration for serially acquired voltammograms, which pose significant demands on the real-time storage capacity and computational power consumption of embedded systems.

2.2.4 | Impedimetry

Electrochemical impedance spectroscopy provides unique interfacial characterization capabilities for continuous monitoring in blood by applying a small-amplitude alternating potential perturbation and measuring the system's impedance response.³⁸ The core strengths of this method lie in its non-destructive nature and rich depth of interfacial information, enabling real-time discrimination between changes in the electrical double layer, charge-transfer processes, and mass-diffusion behavior. Yet this very feature acts as a double-edged sword: because the signal encapsulates a broad spectrum of interfacial events, it is highly susceptible to interference from various factors in blood, such as nonspecific adsorption, making it difficult to extract the target-specific information accurately and to derive physiologically meaningful interpretations.

2.3 | Performance metrics for blood sensing

Following the discussion of the unique blood environment and the corresponding sensing mechanisms, establishing a

set of key performance metrics for quantitative validation is essential. Together, they form a comprehensive evaluation framework for assessing both the technological maturity and clinical applicability of the sensors. This section systematically elaborates the core performance indicators for evaluating implantable electrochemical blood sensors, including sensitivity, selectivity, response time, signal stability, and biocompatibility. These metrics not only reflect the fundamental analytical capabilities of the sensors but also carry specific implications within the context of the blood environment.

2.3.1 | Sensitivity

In the context of blood monitoring, sensitivity is specifically defined as the ratio of the repeatable and distinguishable change in the output signal of an electrochemical sensor to the variation in target analyte concentration within the complex blood matrix. High sensitivity is the fundamental prerequisite for a sensor to capture subtle, dynamic changes in analyte concentration with a high signal-to-noise ratio amidst the high-background-noise blood environment. Under comparable levels of environmental noise, higher sensitivity generally corresponds to a lower practical limit of detection, allowing the sensor to probe lower trace-level and even ultra-trace analytes. To achieve enhanced sensitivity, a multi-level co-design strategy can be applied. At the material level, the design of highly responsive sensing materials, such as catalysts with superior activity, can be employed. At the methodology level, adopting detection principles with intrinsically high signal-to-noise ratios (such as the square-wave voltammetry discussed earlier) can effectively amplify the target signal. At the device-architecture level, for ultra-low-concentration (below picomolar level) analytes, sensors can be constructed by leveraging signal-amplification mechanisms (e.g., the transconductance amplification of organic electrochemical transistors^{39,40}) to enable ultra-high-sensitivity detection.

2.3.2 | Selectivity

Selectivity evaluates the core capability of an electrochemical sensor to specifically recognize and respond to the target analyte while minimizing signal interference from other coexisting substances. Blood contains numerous molecules that share close structural and electrochemical similarities, such as families of amino acids and catecholamines,^{41,42} which differ subtly, even by a single functional group. Thus, high selectivity is the cornerstone for ensuring highly accurate and reliable detection results

in blood monitoring. It directly determines whether the data provided by the sensor possesses clinical validity and decision-guiding value. To achieve outstanding selectivity, designing materials with highly specific recognition sites is crucial. Furthermore, leveraging advanced data-processing algorithms (e.g., machine-learning-driven pattern recognition) to extract the target information from the mixed signals is also a promising method.^{43,44}

2.3.3 | Stability

In blood monitoring, the stability of a sensor refers to its ability to maintain long-term consistency and reliability in output signals during continuous operation or repeated use. Specifically, during continuous monitoring, the sensor exhibits minimal baseline drift and no significant degradation in sensing performance.⁴⁵ High stability serves as the foundation for ensuring coherent and dependable sensing data, while also reducing the need for frequent calibration,⁴⁶ extending service life, and thereby lowering medical consumable costs and operational burdens. Maintaining high stability in implantable electrochemical sensors during blood monitoring is extremely difficult and remains a key focus of current research. There are numerous factors in the blood environment that affect sensor stability. Environmental interference, such as fluctuations in body temperature, pH, and ion concentration, can alter the kinetics of electrochemical reactions and exacerbate signal drift. Additionally, the sensing active material itself may undergo chemical or structural changes over time, leading to performance degradation. Finally, biofouling, such as the nonspecific adsorption of proteins, lipids, and cells onto the electrode surface, can cause electrode passivation, resulting in baseline drift or even sensor failure.

To achieve highly stable sensing, improvements can be pursued on three levels: materials, device design, and signal processing. At the material level, anti-biofouling interfaces can be designed, and intrinsically stable active sensing materials can be selected. In terms of device design, a reference sensing electrode can be incorporated.⁴⁷ This electrode shares a similar structure with the working sensing electrode but does not respond to the target analyte, allowing common-mode interference to be subtracted through differential output. However, in practice, fabricating an entirely ideal reference sensing electrode remains highly challenging. Thus, the method of differentiating the high-frequency and low-frequency signals in SWV was proposed to suppress the drift.⁴⁸ Regarding signal processing, baseline correction algorithms can

be employed to compensate for environmental interference through modeling. In addition, the stability of the reference electrode itself represents an important yet overlooked challenge. In the complex blood environment, maintaining a stable reference potential is critical for accurate measurements, as any drift in the reference electrode directly translates into apparent signal changes that are indistinguishable from true variations in analyte concentration. Although solid-state reference electrodes (e.g., using polyvinyl butyral membranes or other ion-blocking layers) have been developed to improve stability, achieving long-term reliability under continuous blood exposure remains challenging. Developing truly stable and biocompatible reference electrodes for long-term in vivo use requires concerted attention and breakthrough efforts from the research community.

2.3.4 | Response time

Response time refers to the total delay from when a sensor encounters a concentration change to when it outputs a stable signal. Here, we advocate for greater emphasis on evaluating the actual response time of sensors in the blood environment, rather than relying solely on ideal response times measured in simulated solutions, like phosphate-buffered saline. In blood, it is jointly determined by three phases: mass-transport diffusion, interfacial reaction, and signal stabilization, and ultimately reflects the system's ability to track real-time dynamic concentrations in blood. Achieving an optimal response time is not about pursuing absolute speed, but requires a strategic trade-off between response time and other performance metrics based on the intended application scenario. For real-time critical-care alerts (requiring second-level speed, e.g., hyperkalemia detection), thinner mass-transport barriers and sensing mechanisms with high temporal resolution may be employed, albeit potentially at the cost of long-term stability. In contrast, for relatively long-term pharmacokinetic monitoring, an acceptable minute-level delay can be traded for extended service life and improved anti-interference capability. In summary, we stress that, under the premise of precisely matching the time scale of the target physiological process, sensor performance is optimized to best suit the specific clinical scenario.

2.3.5 | Hemocompatibility

Apart from sensing performance, hemocompatibility is another critical evaluation metric for implantable

electrochemical sensors. Hemocompatibility refers to the ability of a material or medical device to maintain the normal physiological state of blood without inducing harmful reactions upon contact. Specifically, after sensor implantation, it must prevent adverse effects such as thrombosis, hemolysis, and systemic inflammatory activation. At the vascular level, the sensor should avoid causing endothelial injury, significantly disturbing local hemodynamics, inducing turbulent flow, or leading to luminal stenosis. Hemocompatibility directly determines the clinical safety risk of the sensor. Therefore, to ensure its biosafety, the subsequent development and application of sensors must strictly adhere to standardized hemocompatibility testing systems (ISO 10993-4).⁴⁹ These systems cover multiple key evaluation criteria, including thrombosis tendency, coagulation function impact, and platelet activation, and require systematic assessment of how compatibility changes over time. For short-term implantation applications, the sensor should demonstrate no significant risk within hours to days. For long-term implantation scenarios, such as indwelling venous catheters, stable compatibility must be maintained for over 3 months. To achieve clinically required hemocompatibility, a dual-strategy approach should be adopted: on one hand, interface materials with properties such as anticoagulation and anti-biofouling must be developed; on the other hand, flexible and miniaturized structural designs for the sensor are essential to reduce mechanical stimulation to blood vessels, minimize hemodynamic disturbance, and thereby enhance long-term stability and biosafety in the blood environment.

3 | MATERIALS AND SYSTEM DESIGN STRATEGIES FOR BLOOD MONITORING

Building on the understanding of the unique electrochemical environment of blood, the development of advanced materials and innovative system architectures is essential to meet the stringent demands and performance criteria for blood sensing. Below, we explore how the design of sensing materials enables high-performance detection of target analytes in blood. At the device level, we further examine how miniaturization, flexibility, and intelligent integration ensure that sensors not only achieve accurate measurements but also seamlessly adapt to the dynamic vascular environment.

3.1 | Sensing materials for blood monitoring

3.1.1 | Biological recognition materials

The recognition element lies at the core of blood sensing (Table 2). Inspired by the fact that living organisms themselves constitute complex systems composed of countless high-precision sensors, where specific molecular recognition, such as neurotransmitter-receptor binding⁵⁰ and immune system pathogen identification,⁵¹ occurs routinely throughout biological processes. Researchers thus initially turned to nature for guidance by harnessing biological recognition elements to develop sensors. Today, the most commonly used biological recognition elements in

TABLE 2 Comparison of recognition materials for in vivo blood monitoring.

Material type	Biological recognition materials		Synthetic recognition materials	
	Enzymes	Aptamers	MIPs	Nanozymes
Recognition mechanism	Specific catalytic reaction with substrate	Conformational change upon target binding	Synthetic recognition sites complementary to the target	Nanomaterials with enzyme-like catalytic activity
Representative applications	Small molecules	Small-molecule drugs, proteins, ions	Small molecules, proteins, cells	Small molecules
Advantages	1. High specificity 2. High sensitivity 3. Well-established technology	1. Broad target applicability 2. Easy for chemical design 3. Better stability than proteins	1. High physicochemical stability 2. Highly tunable performance 3. Cost-effective 4. Easy to prepare	1. High physicochemical stability 2. Scalable synthesis 3. Tunable activity
Limitations	1. Susceptible to proteolysis and immune response 2. Limited lifetime (days) 3. Restricted to endogenous metabolites	1. Susceptible to nuclease degradation 2. Slow binding kinetics	1. Slow binding kinetics 2. Potential template leakage 3. Biocompatibility concerns	1. Lack of selectivity 2. Restricted to the small molecules

Abbreviation: MIPs, molecularly imprinted polymers.

implantable electrochemical sensors for blood monitoring are enzymes and aptamers.

Enzyme-based sensing relies on the specific catalytic reaction of enzymes toward their substrates. This reaction is typically a continuous and reversible chemical process, whose rate reflects real-time changes in substrate concentration. By immobilizing enzymes on the electrode surface, continuous and real-time electrochemical responses to target analyte concentrations can be achieved.⁵² The sensor based on glucose oxidase for glucose monitoring is a classic example of this technology (Figure 2A). After more than 60 years of development, continuous glucose monitoring systems based on glucose sensors have been successfully commercialized and have become a standard tool in diabetes management.^{55,56} Furthermore, researchers have utilized uricase for monitoring blood uric acid, as well as a cascade reaction involving creatinine amidohydrolase, creatine amidohydrolase, and sarcosine oxidase to catalyze the breakdown of creatinine, ultimately generating electroactive species such as H_2O_2 that can be detected by the electrode,⁵⁷ thereby enabling creatinine monitoring. The natural high specificity of enzymes toward their substrates provides sensors with excellent selectivity. However, enzymes are intrinsically proteins and are susceptible to degradation by proteases and immune responses when implanted long-term in vivo, leading to deactivation and significantly limiting the sensor's operational lifetime, typically to just a few days. Moreover, the variety of enzymes suitable for electrochemical sensing in nature is limited, making it difficult to extend this approach to the detection of non-physiological small molecules or macromolecular biomarkers.

Aptamers are DNA or RNA sequences obtained through in vitro screening, capable of folding into specific three-dimensional structures that bind to targets with high affinity and specificity. Upon binding, conformational changes typically alter the electron transfer efficiency at the electrode interface,⁵⁸ thereby modulating the current (Figure 2B). Since the binding between aptamers and their targets is a reversible dynamic equilibrium process, reversible conformational changes enable continuous electrochemical responses to variations in target concentration. The established in vitro Systematic Evolution of Ligands by Exponential Enrichment (SELEX) technology is employed to screen specific DNA/RNA aptamers from nucleic acid libraries that bind to the target with high specificity and affinity. This technique allows for the directed screening of aptamers against diverse molecular targets, including drug molecules, proteins, and ions, ensuring both high specificity and affinity.

By attaching redox reporter molecules (e.g., methylene blue) to aptamers, continuous monitoring of various small-molecule drugs has been achieved (Figure 2C) by

leveraging changes in electron transfer efficiency induced by conformational shifts in the presence or absence of target molecules. Examples include the anticancer chemotherapeutic agent doxorubicin, as well as aminoglycoside antibiotics such as kanamycin, gentamicin, and tobramycin,⁴⁸ covering commonly used therapeutic drugs in clinical practice. Developing sensors based on aptamers offers several advantages. First, aptamers have a broad target applicability. SELEX technology can be used to screen aptamers for almost any target, including non-endogenous molecules that traditional enzymes cannot recognize. Additionally, aptamers can be chemically synthesized in bulk and conveniently modified with reporter groups (e.g., fluorescent or electrochemical tags), facilitating miniaturization and array integration. As nucleic acids, aptamers exhibit better stability than protein-based enzymes. However, nucleases present in the blood can still degrade aptamers, compromising their stability. Furthermore, high-affinity aptamers often exhibit slower binding kinetics, which may affect response times.

In addition, the specific binding between antibodies and antigens can also be utilized to recognize target molecules in the blood. However, antibody-antigen binding is typically an irreversible, high-affinity interaction that often requires the addition of secondary antibodies or washing steps to remove adsorbed antigens.^{39,59} For in vivo implantation, such irreversible binding can lead to rapid saturation of the sensor surface, rendering continuous monitoring unfeasible. Similar challenges exist with other recognition elements, such as lectins⁶⁰ and epitopes.⁶¹

3.1.2 | Synthetic recognition materials

Although significant progress has been made in implantable sensors based on enzymes and aptamers, their inherent biological limitations, particularly their susceptibility to biodegradation within the body, constrain their long-term in vivo application. This limitation has shifted research focus toward synthetic recognition elements. These materials are artificially designed to combine biomimetic recognition capabilities with the physicochemical stability of synthetic systems, offering the potential to overcome the lifespan constraints of biological components.

Among these synthetic alternatives, molecularly imprinted polymers (MIPs) stand out as a prime example of biomimetic design. Often termed “artificial antibodies,” MIPs are engineered to mimic the exquisite specificity of biological recognition while being composed entirely of robust synthetic polymers.⁶² During its preparation, the template molecules and functional monomers first undergo pre-assembly via non-covalent interactions,

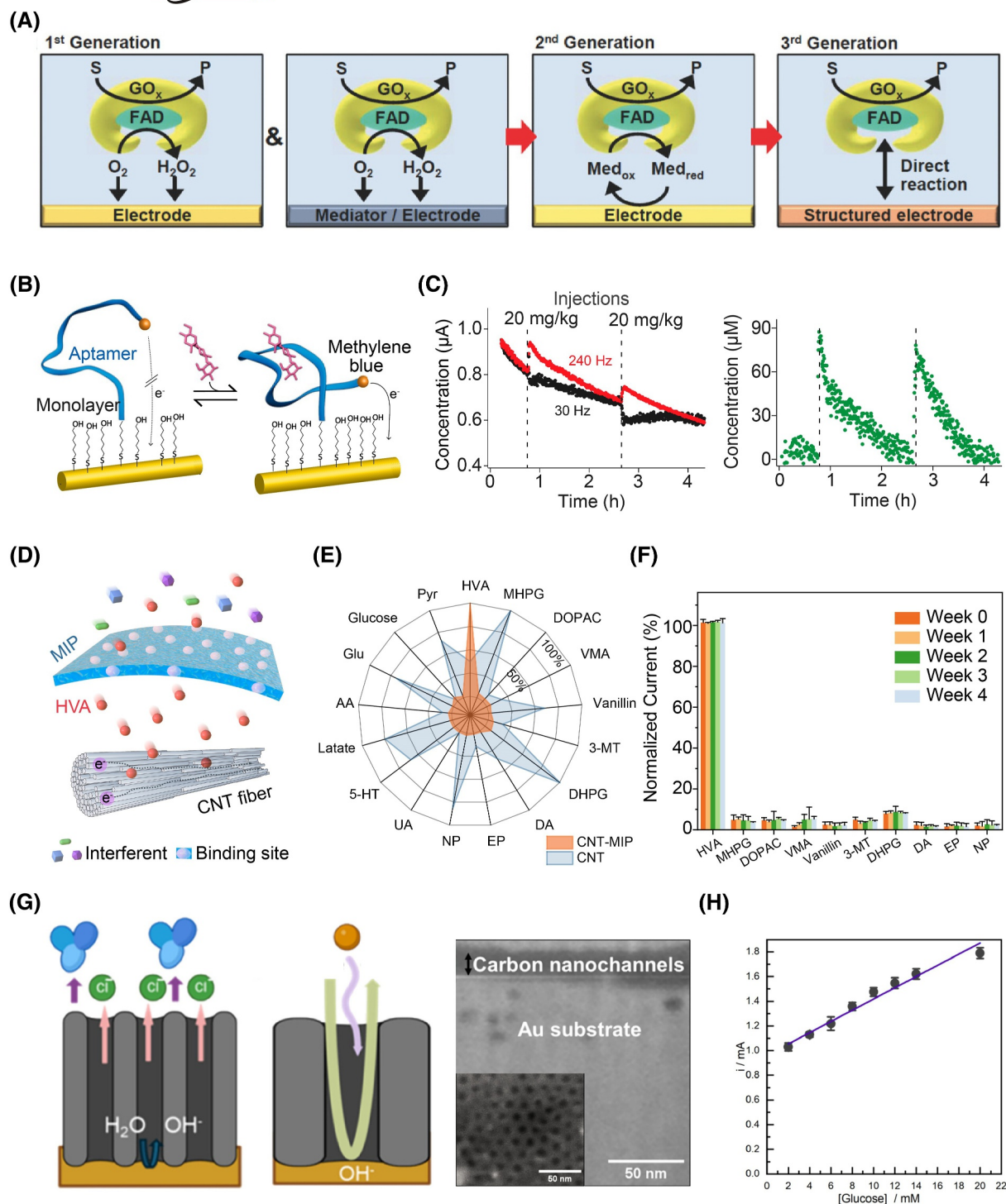


FIGURE 2 Schematics and performance of the recognition materials. (A) Schematic illustration of the evolution of glucose oxidase-based electrochemical glucose sensors.⁵³ Copyright 2018, John Wiley and Sons. (B) Schematic illustration of the aptamer-based sensing principle. Copyright 2017, National Academy of Sciences. (C) Continuous monitoring of drug concentration in blood following successive administration via high- and low-frequency square-wave voltammetry.⁴⁸ Copyright 2017, National Academy of Sciences. (D) Schematic illustration of the MIPs-based sensing principle. Copyright 2024, American Chemical Society. (E) Comparison of the selectivity of sensors with and without MIPs modification. Copyright 2024, American Chemical Society. (F) Long-term stability of selectivity for MIPs-based sensors.⁴¹ Copyright 2024, American Chemical Society. (G) Schematic illustration of glucose nanozyme sensing principle and corresponding scanning electron microscope images. Copyright 2025, American Chemical Society. (H) Calibration curve of the nanozyme-based glucose electrochemical sensor.⁵⁴ Copyright 2025, American Chemical Society.

followed by polymerization in the presence of a cross-linking agent. Finally, the template molecules are removed through physical or chemical methods,⁶³ leaving behind highly specific recognition sites on the polymer membrane that match the template molecules in both physical and chemical environments.⁶⁴ When multiple chemical substances are present, only the target molecules can bind to the recognition sites, thereby significantly enhancing the selectivity of the sensing system (Figure 2D). For instance, with the incorporation of MIPs, the sensor's response to the target molecule is more than 12.6 times greater than its response to interfering substances, even when the interfering substance differs from the target by only a single functional group.⁴¹ In contrast, electrodes without MIPs modification exhibit almost no selectivity (Figure 2E).

The design of sensors based on MIPs is highly flexible and can be categorized, based on their principles, into direct detection and indirect monitoring types.⁴² Direct monitoring is typically suitable for electroactive molecules or molecules that can undergo catalytic reactions. Here, the MIP serves as a selective layer, and after the target molecules adsorb onto the MIP, subsequent electrochemical reactions generate specific redox currents for monitoring. Indirect monitoring is generally used for non-electroactive molecules. In this approach, a redox reporter, such as Prussian blue, is introduced between the MIP and the electrode. The adsorption of target molecules onto the MIP reduces the contact between the redox reporter and the solution, thereby decreasing the redox current to achieve monitoring. By incorporating multiple template molecules during preparation, simultaneous monitoring of multiple analytes can even be achieved. Furthermore, for the adsorption of target molecules onto MIPs, electrochemical methods can be employed to regenerate the recognition sites,⁶⁵ for instance, by applying a potential to drive consumption reactions or electrostatic repulsion, thereby enabling continuous *in vivo* monitoring.

Due to their nature as synthetic polymers, MIPs exhibit excellent physicochemical stability, with a theoretical lifespan far exceeding that of biological components (Figure 2F). Additionally, MIPs hold significant cost advantages over biological elements, and their synthesis process is relatively simple, enabling easy large-scale production. Notably, sensors prepared via electrochemical polymerization demonstrate good batch-to-batch reproducibility. Moreover, MIPs offer broad applicability, as they can theoretically be customized for any target, from small molecules to proteins, and even cells. Despite these advantages, MIPs still face certain limitations in practical

use. Firstly, their binding kinetics are relatively slow, requiring a certain amount of time from the adsorption of target molecules to the establishment of equilibrium and the generation of a stable electrochemical response, which constrains the sensor's response time. The elution of template molecules poses another difficulty, as incomplete removal leads to high background signals. Lastly, their biocompatibility is generally inferior to that of biological recognition elements, necessitating the careful selection of biocompatible monomers and cross-linking agents or surface biofunctionalization modifications.

In addition to MIPs, nanozymes represent another promising class of biomimetic catalytic materials. Nanozymes typically refer to nanomaterials possessing catalytic functions similar to those of natural enzymes.^{66,67} Leveraging the size effects, surface properties, and tunable catalytic active sites of nanomaterials,^{68,69} they mimic the ability of enzymes to efficiently catalyze substrate reactions under specific conditions, thereby generating detectable signals. A representative example is the carbon nanochannel array directly constructed on a gold electrode surface (Figure 2G). Through precise nanoconfinement effects and electrochemical pulse modulation, this structure creates a localized high-pH alkaline microenvironment at the channel bottom, effectively simulating the catalytic function of glucose oxidase under alkaline conditions.⁵⁴ This nanoconfined catalysis strategy enables efficient glucose catalysis in whole blood under enzyme-free conditions, achieving a sensitivity of 40 mA M^{-1} (Figure 2H). The main advantages of nanozymes lie in their excellent physicochemical stability, scalability in synthesis, low cost, and tunable catalytic activity. Compared to natural enzymes, they are less prone to denaturation and inactivation, making them more suitable for long-term, continuous monitoring in harsh environments. However, limitation exists in their insufficient selectivity toward small molecules with similar structures and activities, as catalytic sites may act on multiple substrates simultaneously, leading to susceptibility to interference in complex biological samples. A feasible strategy is to integrate nanozymes with the aforementioned MIPs. By constructing a selective MIPs layer on or around the surface of a nanozyme, the high-specificity recognition sites provided by MIPs prescreen target molecules, enabling them to preferentially access the catalytically active centers of the nanozyme. In this way, MIPs contribute high selectivity, while nanozymes provide stable and efficient catalytic function. By combining their complementary strengths, it is possible to develop a next-generation biomimetic sensing platform that integrates high selectivity, high stability, and rapid response.

3.1.3 | Antifouling sensing interface construction

When exposed to blood, the sensing interface is easily fouled by the nonspecific adsorption of proteins and blood cells, which on the one hand causes the formation of biofilm on the sensor surface, leading to degradation of the sensing performance; On the other hand, it may serve as a site for the coagulation cascade to promote the formation of thrombi in the long term. To resolve this issue, antifouling interfaces have thus been constructed to minimize biofouling and ensure accurate electrochemical detection. Existing antifouling strategies can be categorized into three classes according to their underlying mechanisms: physical barrier strategies, surface chemical modification strategies, and antifouling/sensing synergistic strategies.

Physical barrier strategies: Physical barrier strategies leverages size exclusion, allowing small-molecule targets to pass through while blocking access of larger molecules and cells in the blood. This is typically achieved by creating a pore structure with specifically designed pore sizes. By encapsulating an electrochemical aptamer sensor within a biocompatible polysulfide membrane with 0.2 μm pores, blood cells can be prevented from reaching the sensor surface without impeding the rapid transport of target molecules.⁴⁸ Furthermore, inspired by the microvillar structure of the intestinal mucosa, researchers have developed a three-dimensional bicontinuous nanoporous gold substrate with pores as small as 17 nm (Figure 3A). Coupled with a surface coating of hyperbranched polyethylene glycol (PEG) that forms a dense polymer brush,⁷⁰ this structure can immobilize aptamers shorter than 10 nm while effectively blocking the nonspecific adsorption of red blood cells and larger plasma proteins (Figure 3B).

Surface chemical modification strategies: Although physical barriers block macromolecules, they cannot effectively prevent the adsorption of small-molecule proteins or biofouling at the interface. Surface chemical modification strategies address this by altering the physicochemical properties of the interface to inhibit nonspecific interactions. PEG and zwitterionic hydrogels have been extensively studied and are regarded as classical antifouling materials and benchmarks.⁷⁴ The numerous ether bonds in PEG molecular chains form multiple hydrogen bonds with water molecules, constructing a dynamic and dense hydration layer.⁷⁵ This hydration layer repels the approach of contaminants such as proteins and cells. Zwitterionic hydrogel molecules,^{76,77} on the other hand, contain equal amounts of positive and negative charges (e.g., phosphorylcholine or sulfobetaine groups). Through strong electrostatic interactions, they tightly bind water molecules and resist influences from environmental

changes (e.g., ionic strength or pH), forming an ionic hydration layer that is more stable than that of PEG.

Building upon this foundation, to develop more advanced antifouling coatings, Chan et al. employed machine learning to conduct high-throughput screening of a library of 172 binary copolymer hydrogels constructed from 11 acrylamide-based monomers.⁷⁸ They discovered that a 50:50 copolymer of hydroxyethyl acrylamide and diethylacrylamide exhibited the best performance, with a platelet adhesion count of only 82.0 ± 15 cells cm^{-2} , far superior to that of PEG (4810 ± 520 cells cm^{-2}). Coating this hydrogel onto the surface of an electrochemical sensor significantly extended its functional lifespan to 5 days. Additionally, combining physical size exclusion with surface chemical interactions is also an effective strategy.⁷¹ By tailoring the mesh size of agarose hydrogels and leveraging the abundant hydroxyl groups in agarose that form a dense hydration layer via hydrogen bonding with water molecules (Figure 3C), the diffusion of plasma proteins and blood cells is significantly suppressed. Calculations based on the Amsden model indicate that the diffusion coefficient of fibrinogen within the gel is merely 1.1×10^{-4} of its value in free solution, rendering it nearly incapable of penetrating the gel barrier (Figure 3D).

Antifouling/sensing synergistic strategies: The aforementioned antifouling coatings have been proven effective in suppressing nonspecific adsorption. However, their incorporation often inevitably impedes the interaction between recognition elements and target molecules, thereby compromising sensing performance. This typically manifests as a significant attenuation in sensitivity and an increase in response time. Antifouling/sensing synergistic strategies aim to resolve this inherent trade-off by combining antifouling properties with electrochemical functionality.

A notable example is the development of a 3D matrix composed of glutaraldehyde cross-linked bovine serum albumin (BSA) interlaced with conductive gold nanowires (Au NWs) (Figure 3E). This hybrid coating combines a porous BSA hydrogel (with an average pore radius of 29 ± 3 nm) with a hydrophilic interface that not only acts as a physical barrier but also resists nonspecific protein adsorption, maintaining 88% of the original signal after 1 month of exposure to unprocessed human plasma.⁷² In the meantime, the incorporation of Au NWs establishes a conductive network, which effectively enhances electron transfer efficiency. This approach achieves antifouling performance while maintaining 92% of the electrochemical performance of a bare gold electrode (Figure 3F), thereby successfully balancing antifouling capability with electrochemical functionality. The introduction of multi-scale pore design further balances the requirements for mass transport and antifouling. Using the emulsion

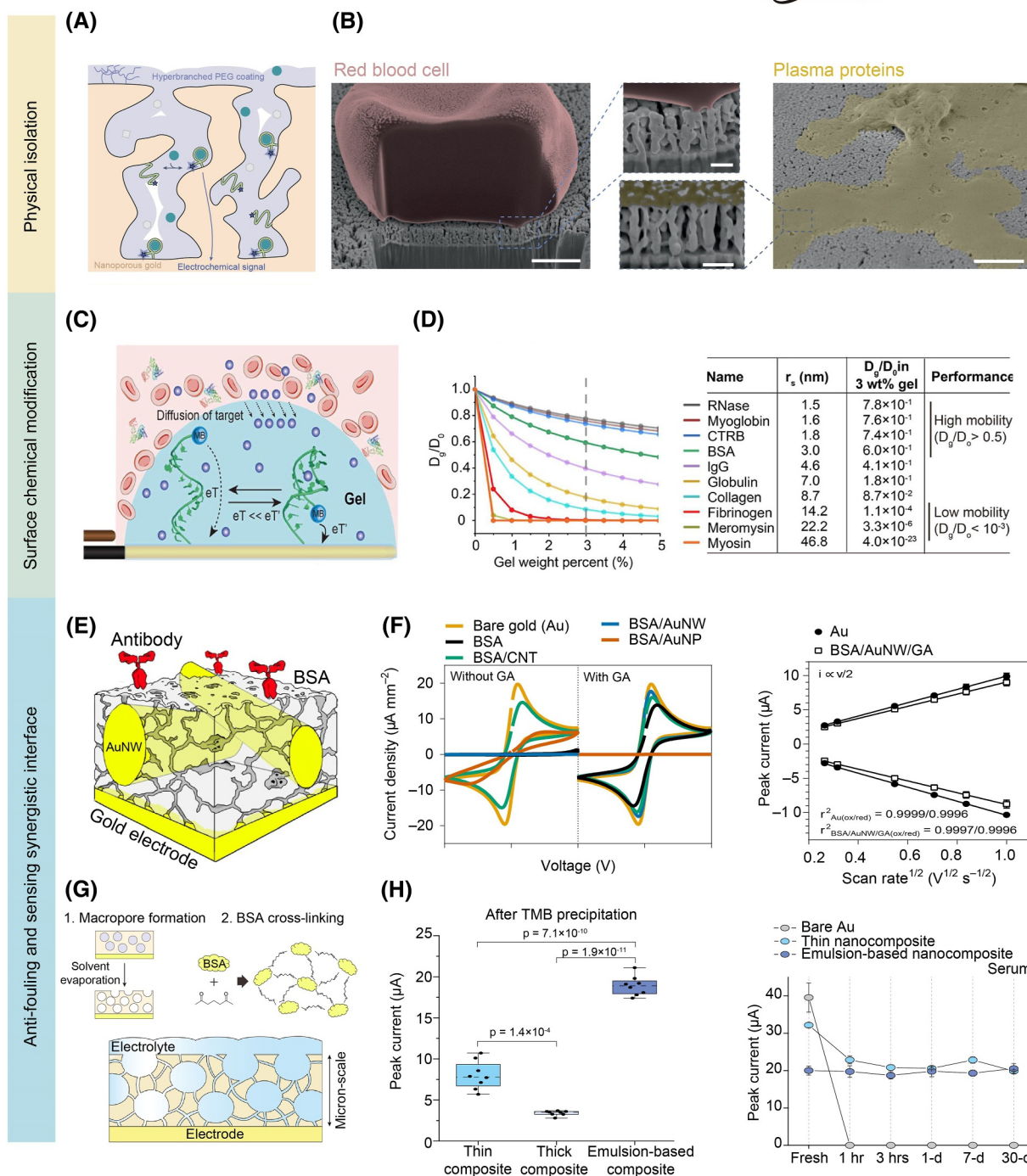


FIGURE 3 Strategies for constructing anti-fouling interfaces. (A) Schematic illustration of nanoporous gold for blocking proteins and blood cells. Copyright 2025, Springer Nature. (B) Scanning electron microscope images of the nanoporous gold against red blood cells and plasma proteins.⁷⁰ Copyright 2025, Springer Nature. (C) Agarose hydrogel-based anti-fouling interface. Copyright 2023, American Chemical Society. (D) Modeling the impact of agarose hydrogel on protein diffusion constants based on Amsden's theoretical framework (D_g/D_0 represents the diffusion constant in gel relative to that in free solution).⁷¹ Copyright 2023, American Chemical Society. (E) A 3D matrix composed of glutaraldehyde-crosslinked bovine serum albumin intertwined with conductive gold nanowires for simultaneous anti-fouling and enhanced electron transport. Copyright 2019, Springer Nature. (F) Redox peak currents of nanocomposite-modified electrodes in 5 mM ferri-/ferrocyanide solution (left) and extracted peak current versus the square root of scan rate (right).⁷² Copyright 2019, Springer Nature. (G) An internally interconnected hierarchical pore system allowing for simultaneous anti-fouling and rapid diffusion of small molecules. (H) Redox peak currents of different composite modified electrodes in a 5 mM ferri-/ferrocyanide solution post-3,3',5,5'-tetramethylbenzidine precipitation reaction (left) and after 1-month storage in serum (right).⁷³

templating method, a micrometer-thick porous BSA/AuNW coating was fabricated (Figure 3G). Its internally interconnected micropores ($\sim 1.1 \mu\text{m}$) and nanopores ($\sim 9.5 \text{ nm}$) form a hierarchical pore system, which not only provides rapid diffusion pathways for small-molecule targets and electroactive species but also effectively blocks larger foulant molecules.⁷³ With a thickness of approximately $1 \mu\text{m}$, this coating provides a robust antifouling performance far exceeding that of a nanoscale coating while maintaining electrochemical sensing capabilities comparable to the thin coatings. As a result, sensors fabricated with this coating exhibited stable peak currents after 1 month of immersion in serum, significantly outperforming both thin-film coatings and unmodified electrodes (Figure 3H).

Summary: Three major categories of antifouling strategies have been developed to address the challenges posed by the blood environment. Physical barrier strategies rely on size exclusion to prevent macromolecules and cells from reaching the electrode surface, offering a straightforward and effective means of blocking macroscopic foulants, yet they fail to prevent the adsorption of small proteins. Surface chemical modification strategies alter the physicochemical properties of the sensor surface to create hydration layers that resist nonspecific interactions at the molecular level, providing broad protection but at the cost of significantly compromised sensing performance. Antifouling/sensing synergistic strategies aim to simultaneously achieve high electrochemical performance and robust antifouling capability. By integrating conductive networks with antifouling matrices or designing hierarchical pore structures, these approaches effectively mitigate the inherent trade-off between surface passivation and signal transduction. With successful antifouling interface design, long-term in vivo blood monitoring becomes feasible.

3.2 | Sensor architectures for the intravascular blood monitoring

Advancements in recognition elements and anti-fouling interfaces have laid the foundation for high-performance blood sensing. However, designing suitable carriers for these sensing materials to form implantable devices, thereby enabling them to function effectively in the bloodstream, is equally crucial. This requires implantable sensors to be highly compatible with the one-dimensional and confined vascular environment. This section discusses sensor architectures for intravascular blood monitoring from the perspective of sensor carriers, which can be classified into two categories: standalone sensors for

intravascular implantation and sensors integrated with intravascular medical devices.

3.2.1 | Standalone sensors for intravascular implantation

To align well with the geometry of blood vessels, sensors for intravascular blood monitoring are expected to exhibit a miniaturized and one-dimensional structure.^{79–81} The most straightforward approach involves utilizing the excellent electrical conductivity and mechanical strength of metal wires for sensing. A representative study constructed a three-electrode system based on metal wires, in which functionalized gold, platinum, and silver wires served as the working, counter, and reference electrodes, respectively (Figure 4A). These wires were bundled and secured using heat-shrink tubing, with the overall diameter comparable to that of a 22 G catheter needle.⁴⁸ After surgically exposing the target blood vessel (such as the femoral vein), this microwire probe could be directly inserted and implanted into the vascular lumen (Figure 4B), similar to a conventional guidewire. Although this design achieves in vivo monitoring, its rigid nature may cause friction against the vascular endothelium or elicit strong foreign body reactions in surrounding soft tissues due to mechanical mismatch, thereby limiting its long-term application and patient comfort.^{84,85}

To address the limitations of mechanical mismatch, the development of flexible fiber electrodes has become an urgent priority. A groundbreaking study, inspired by hierarchical biological tissues such as muscles, developed a carbon nanotube (CNT) fiber electrode with a hierarchical oriented structure (Figure 4C). Due to this hierarchical design, the CNT electrode achieves bending stiffness ($5.66 \times 10^{-9} \text{ nN m}^2$) compatible with soft biological tissues and about six orders of magnitude lower than metal wires,⁸² allowing it to be easily wrapped around thin rods (Figure 4D). At the same time, it retains the high conductivity (10^4 S cm^{-1}) and large electrochemically active surface area ($850 \text{ cm}^2 \text{ g}^{-1}$) inherent to CNT, making it an ideal material for sensing electrodes.⁸⁶ After functionalization, the resulting flexible fiber sensor can be minimally invasively implanted into a vessel via percutaneous venous injection using a standard syringe (Figure 4E). The fiber sensor also demonstrated excellent biocompatibility, forming a compatible interface with vascular tissue (Figure 4F) and showing no adverse effects on blood flow velocity after 4 weeks of implantation in a rat vein (Figure 4G).

Leveraging this innovation, a series of implantable electrochemical fiber sensors has been developed, monitoring indicators including H_2O_2 , prostate-specific antigens,

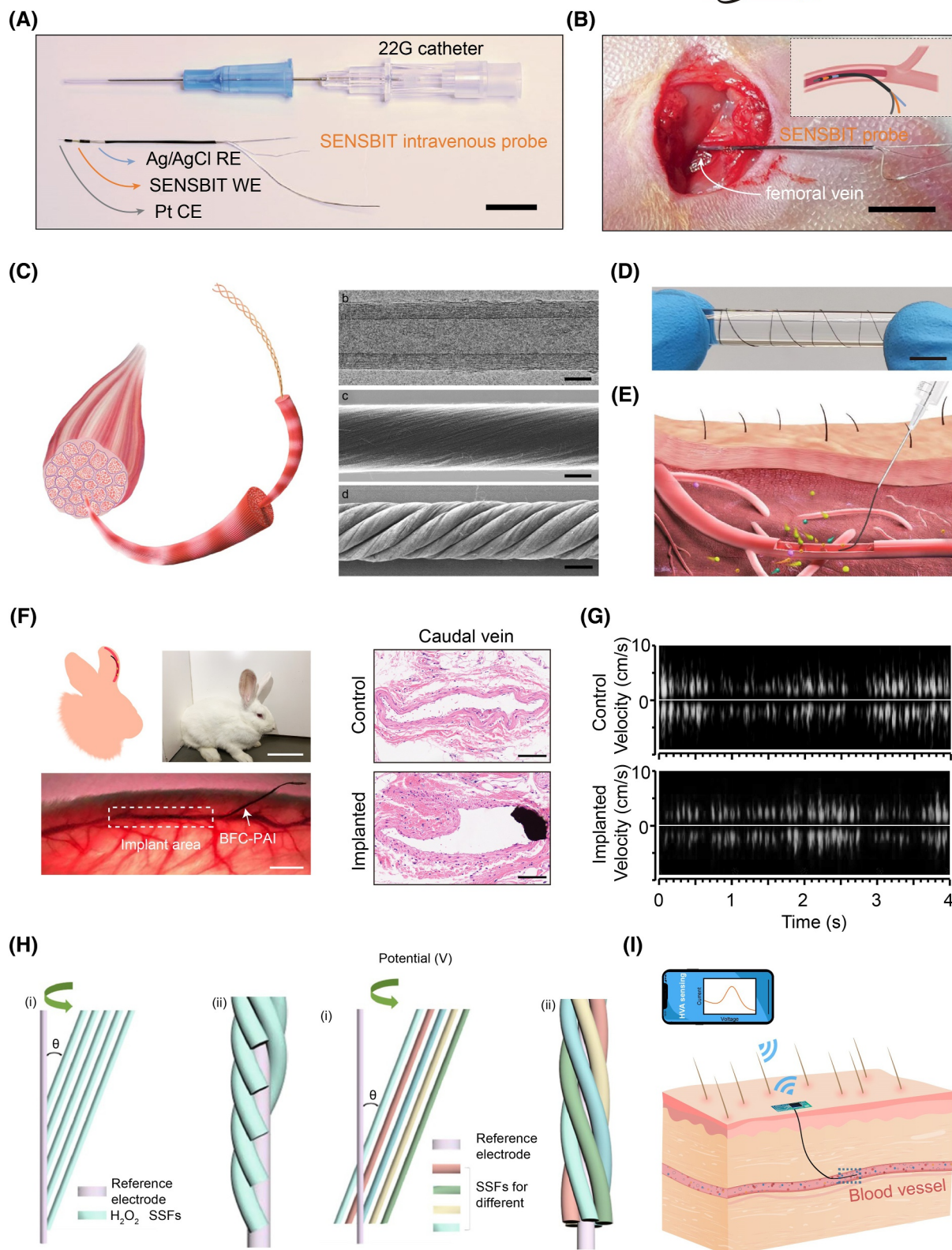


FIGURE 4 Legend on next page.

calcium ions, pH, glucose, and homovanillic acid (HVA), with high sensitivity and temporal resolution. Meanwhile, the unique one-dimensional fibrous structure also enables it to be integrated by spiral twisting for spatially distributed

and multi-functional sensing (Figure 4H). Following implantation, the fiber end exposed on the skin can be connected to a flexible chip, enabling real-time processing of sensing signals and wireless transmission to mobile

terminals (Figure 4I). This constitutes a complete continuous monitoring system, demonstrating broad application prospects in precision medicine and disease management.

3.2.2 | Sensors integrated with intravascular medical devices

Compared with developing standalone sensors, the design of directly integrating sensors with established intravascular medical devices eliminates the need for additional implantation procedures.⁸⁷ Instead, it seamlessly embeds sensing functionality into existing clinical workflows,⁸⁸ equipping medical tools with in situ, real-time monitoring capabilities while minimizing interference with standard medical operations.^{89,90}

As shown in Figure 5A, Guan et al. proposed an iontronic tip-sensing guidewire, which integrates an iontronic sensor at its tip. This sensor utilizes the electric double layer formed at the interface between a metal tip and a microstructured ionic gel layer to convert intravascular pressure into a capacitance signal. Notably, it leverages the ionic conductivity of human tissues and blood as the signal transmission medium, eliminating the need for additional embedded conductive leads. In contrast to commercial pressure guidewires, which typically integrate optical or piezoresistive sensors and often compromise torque transmission efficiency (i.e., maneuverability), this iontronic guidewire largely preserves the core structure of the original guidewire. This enables it to maintain an ideal torque ratio of 1:1 and excellent torsional stiffness, significantly surpassing conventional commercial pressure guidewires in terms of maneuverability and pushability within tortuous vessels. The iontronic tip-sensing guidewires were then used for in vivo monitoring of distal pressure to measure the fractional flow reserve (FFR) (Figure 5B), offering a highly promising alternative to traditional guidewires.

In addition to guidewires, venous catheters also serve as a broad platform for sensor integration.⁹² A recent study

utilized 4D multichannel printing technology to develop a magnetically actuated multimodal bioelectronic catheter (Figure 5C). Featuring a multichannel-sheath structure, this catheter was fabricated in a single step by printing liquid metal microchannels (for electrical conduction) and a central hollow lumen (for drug delivery) within a polydimethylsiloxane matrix doped with neodymium iron boron magnetic particles. Sensing microelectrode arrays are integrated at the ends of the liquid metal channels to enable multimodal monitoring. Under an external magnetic field, the catheter can undergo large-angle bending, achieving active magnetically controlled navigation (Figure 5D). This capability allows the catheter to navigate through various complex vascular phantoms, perform multifunctional in situ blood biochemical monitoring (Figure 5E), and simultaneously enable controlled drug or contrast agent delivery via the central lumen, thereby preliminarily realizing the integration of diagnosis and therapy.

Integrating sensors with intravascular medical devices represents a crucial step toward the clinical translation of implantable blood monitoring technologies. This strategy leverages the established operational workflows and implantation pathways of existing devices, eliminating the need for additional implantation procedures. As a result, it offers higher clinical acceptance and a shorter translation pathway while simultaneously empowering conventional tools with intelligence. This approach provides a highly promising solution for achieving precise and safe personalized surgical interventions.

There are also other device architectures for blood monitoring, such as microneedle-based technologies that indirectly monitor blood via interstitial fluid, point-of-care microfluidic systems based on ex vivo blood sampling, optical methods for non-invasive or minimally invasive blood monitoring, and extravascular sensors for blood pressure monitoring. These are not included in the discussion of this section because they cannot be implanted in blood vessels for direct blood contact and continuous electrochemical monitoring.

FIGURE 4 Standalone sensors for intravascular implantation. (A) The intravenous probe based on metal wires. Copyright 2025, Springer Nature. (B) The intravenous probe implanted into an exposed femoral vein.⁷⁰ Copyright 2025, Springer Nature. (C) A hierarchically aligned carbon nanotube fiber electrode inspired by multilayered muscle tissue.⁸² Copyright 2019, Springer Nature. (D) The flexible fiber sensor wound around a glass rod.⁴¹ Copyright 2024, American Chemical Society. (E) Intravenous implantation of the flexible fiber sensor via syringe injection.⁸² Copyright 2019, Springer Nature. (F) Implantation of a flexible fiber sensor into the marginal ear vein of a New Zealand rabbit.⁸³ Copyright 2018, John Wiley and Sons. The implanted fiber sensor forms a compatible interface with the surrounding Vessel.⁴¹ Copyright 2024, American Chemical Society. (G) No significant effect of the implanted fiber sensor on blood flow velocity.⁴¹ Copyright 2024, American Chemical Society. (H) The integration of fiber sensors via helical twisting for spatially resolved and multifunctional sensing.⁸² Copyright 2019, Springer Nature. (I) Integration of the implanted fiber sensor with a flexible chip to construct a blood monitoring system.⁴¹ Copyright 2024, American Chemical Society.

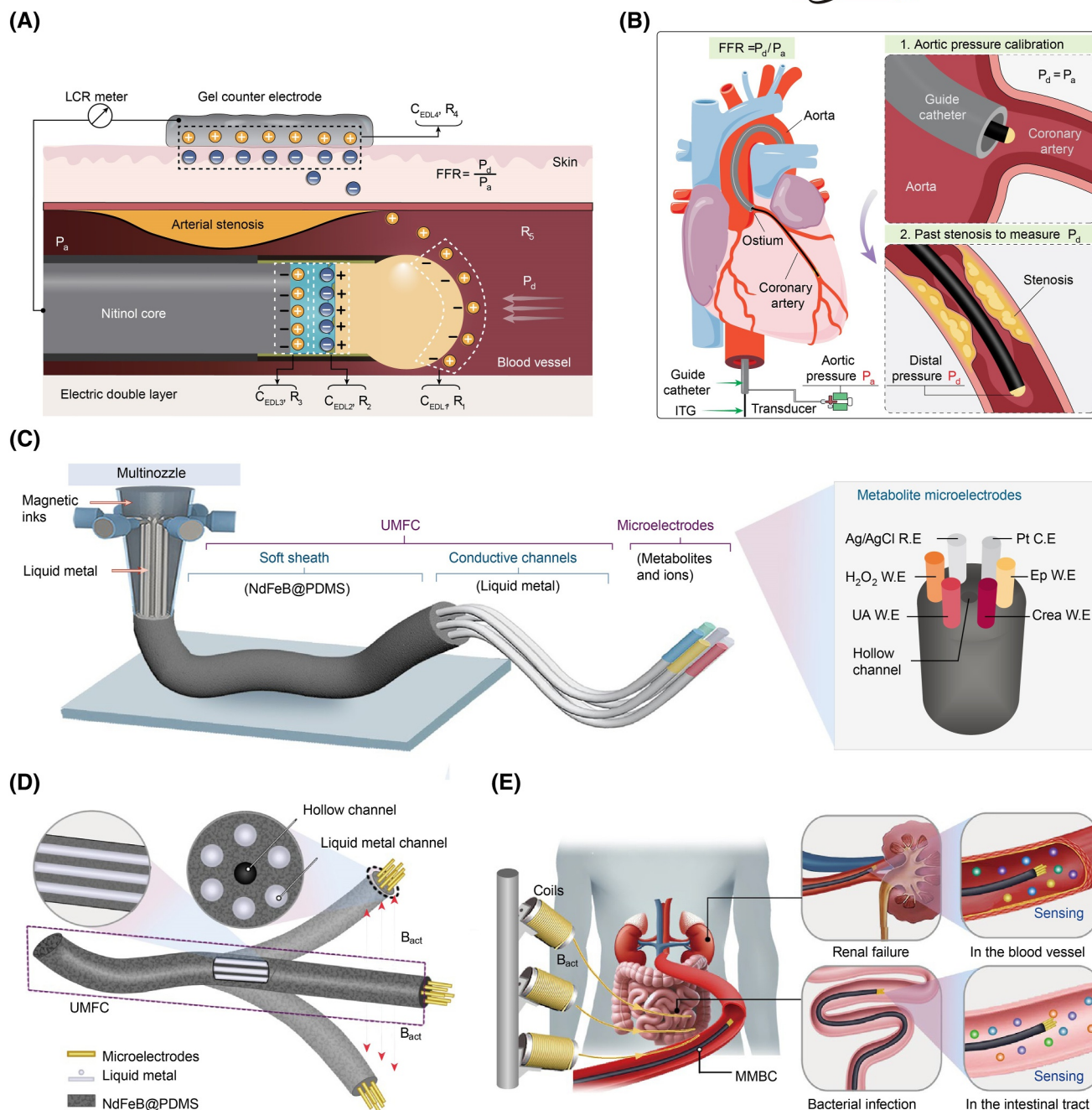


FIGURE 5 Electrochemical sensors integrated with intravascular medical devices. (A) Tip-integrated iontronic sensor on a guidewire. Copyright 2025, Springer Nature. (B) The sensing guidewire advancing into a vascular stenosis for blood pressure monitoring.⁹¹ Copyright 2025, Springer Nature. (C) A 4D-printed multi-channel catheter with an integrated multifunctional microelectrode array on the tip. Copyright 2025, Springer Nature. (D) Magnetically actuated deformation of the catheter. Copyright 2025, Springer Nature. (E) Magnetically guided navigation of the catheter enabling deep tissue access for local blood monitoring.⁵⁷ Copyright 2025, Springer Nature.

4 | APPLICATION OF IMPLANTABLE ELECTROCHEMICAL SENSOR IN BLOOD

4.1 | Physiochemical blood monitoring for intraoperative care

The continuous blood monitoring capability of implantable electrochemical sensors is particularly critical in

time-sensitive and decision-intensive surgical settings. It not only provides immediate data for real-time evaluation of surgical outcomes but also enables in situ, real-time sensing of the physiological and chemical state within the local microenvironment of deep tissues. This advancement facilitates closed-loop control over the surgical process, serving as a key driver for enhancing surgical precision, success rates, and patient safety.

Coronary artery intervention serves as a typical application scenario. Coronary artery disease, affecting tens of millions globally each year,⁹³ is characterized by the accumulation of plaque within the coronary arteries, leading to vessel narrowing that severely restricts blood supply to the heart muscle and ultimately triggers life-threatening heart attacks. FFR measurement provides a critical minimally invasive means to assess the physiological significance of coronary stenoses.⁹⁴ By integrating an iontronic sensor at its tip, this smart guidewire enables precise arterial pressure measurement distal to the stenosis based on the electrochemical double-layer capacitance variation. Once implanted, the guidewire captures real-time, periodic blood pressure pulse waveforms. Researchers simulated vessel stenosis and reperfusion in pig models through balloon inflation and deflation (Figure 6A). Experiments demonstrated that the guidewire successfully monitored a significant drop in distal pressure upon balloon inflation (corresponding to a decrease in FFR from 0.94 to 0.56) and subsequent pressure recovery after deflation, validating its effectiveness in functionally assessing stenosis severity. Furthermore, the guidewire exhibited high sensitivity and rapid response to pharmacologically induced hemodynamic changes. Following an initial injection of a small dose of nitroglycerin (0.5 mL), the guidewire detected a subtle pressure drop of approximately 1 mmHg. After a second dose (1 mL), it identified significant hemodynamic shifts within about 30 s (Figure 6B).

Beyond pressure monitoring, the smart guidewire also features contact force sensing. Abnormal capacitance signals are generated when the guidewire tip contacts the vessel wall, providing immediate warning for the operator to adjust its orientation, thereby effectively reducing the risk of vascular injury, dissection, or perforation.⁹⁵ By delivering real-time physiological data (pressure and contact force), this sensor-integrated smart guidewire significantly enhances the operator's real-time detection capability and decision-making basis during coronary procedures. It represents an innovative tool for improving surgical precision and patient safety.

Besides hemodynamic signals, fluctuations in the local biochemical environment during major surgeries are also critical for assessing organ function and procedural outcomes.⁹⁶ For instance, in kidney transplantation, the donor kidney is susceptible to ischemia-reperfusion injury during procurement, perfusion, and reimplantation.^{97,98} Real-time changes in local metabolites (e.g., creatinine, uric acid) and stress markers (e.g., hydrogen peroxide, norepinephrine) directly reflect graft viability and early functional recovery,⁹⁹ which cannot be timely and accurately captured through systemic blood sampling.⁵⁷

To meet this need, the magnetically actuated multimodal bioelectronic catheter offers a promising solution. As shown in Figure 6C, this catheter can be actively navigated via an external magnetic field to deep target sites (e.g., the renal vein) and perform synchronous, real-time, and continuous monitoring of multiple key indicators (Figure 6D), including metabolites (creatinine, uric acid, H_2O_2 , norepinephrine) and electrolytes (K^+ , Na^+ , Ca^{2+} , pH). This capability not only enables chemical dynamics of organ perfusion and metabolic status but also provides objective, precise data to guide intraoperative fluid management and immediate evaluation of surgical efficacy. By delivering continuous, in situ, and multidimensional data on the local microenvironment, the medical devices integrated with sensors fundamentally enhance the surgeon's real-time perception of pathophysiology. Thereby, they facilitate a paradigm shift from experience-based to data-driven decision-making in the operating room.

4.2 | Blood pharmacokinetic monitoring for precision dosing

In addition to short-term intraoperative monitoring, implantable electrochemical sensors also demonstrate critical application value in longer-term pharmacokinetic monitoring of blood. Blood pharmacokinetic monitoring is a critical measure for preventing drug toxicity and ensuring patient safety.^{100,101} This is especially pertinent for drugs with a narrow therapeutic window, where the effective concentration is very close to the toxic concentration—a hallmark of many chemotherapeutic agents, such as methotrexate,^{102–104} paclitaxel,¹⁰⁵ and cisplatin.¹⁰⁶ If drug concentrations exceed the safe range, severe adverse reactions like myelosuppression, hepatorenal injury, or neurotoxicity may occur. Conversely, subtherapeutic concentrations can lead to treatment failure and inadequate suppression of tumor progression. Continuous monitoring enables precise maintenance of drug levels within the therapeutic window, thereby preventing toxicity from accumulation or loss of efficacy from insufficient exposure. Furthermore, significant interindividual variability in drug absorption, distribution, metabolism, and excretion arises due to factors such as age, hepatic or renal impairment, and pregnancy.^{107–109} Pharmacokinetic monitoring provides a reliable basis for scientifically adjusting dosage regimens in these special populations, effectively mitigating the clinical risks associated with empirical dosing.

Traditional pharmacokinetic studies rely on discrete blood sampling and offline analysis, offering low temporal resolution, an inability to capture rapid dynamic changes, and frequent sampling easily causing stress

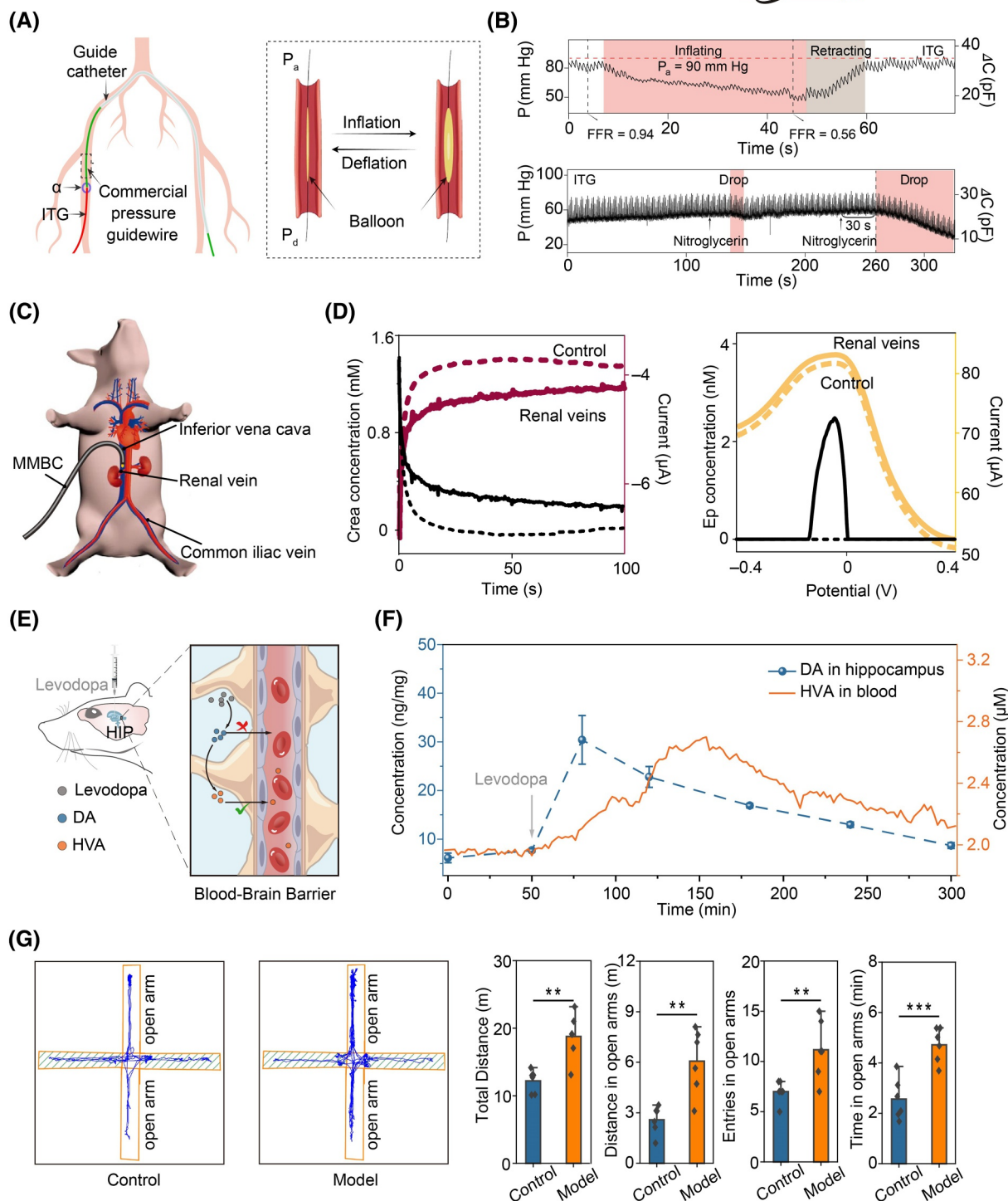


FIGURE 6 Application of the implantable electrochemical sensor in blood monitoring. (A) Schematic illustration of an in vivo vascular stenosis model created by balloon inflation. Copyright 2025, Springer Nature. (B) Continuous blood pressure data from the sensing guidewire under balloon inflation/deflation and post-nitroglycerin conditions.⁹¹ Copyright 2025, Springer Nature. (C) Magnetically guided and multifunctional catheter for blood monitoring in the renal vein. Copyright 2025, Springer Nature. (D) Continuous monitoring of small-molecule metabolites in the renal vein by the catheter.⁵⁷ Copyright 2025, Springer Nature. (E) Schematic illustration of the metabolic pathway of levodopa in vivo. Copyright 2024, American Chemical Society. (F) Continuous monitoring of HVA in blood and its correlation with cerebral dopamine. Copyright 2024, American Chemical Society. (G) Behavioral changes in rats as indicated by continuous blood HVA monitoring.⁴¹ Copyright 2024, American Chemical Society. HVA, homovanillic acid.

interference in animals. Through the development of implantable electrochemical sensors, researchers can perform continuous, real-time, and high-frequency drug concentration monitoring in freely moving animals over several days or even longer periods. Continuous blood drug concentration monitoring has improved temporal resolution by several orders of magnitude, thereby not only enabling the precise capture of the entire process of drug absorption, distribution, and metabolism *in vivo* for the first time but also revealing individual differences difficult to detect with conventional methods. For instance, research results indicate differences in pharmacokinetics between different animals and between multiple injections in the same animal following repeated administration of the antibiotic tobramycin.⁴⁸ This high temporal resolution continuous monitoring capability provides robust technical support for understanding the real-time kinetics of drug action, optimizing dosing regimens, and achieving personalized precision dosing.

Beyond direct monitoring of the drug itself, monitoring drug metabolites is also of great significance. Levodopa is a common therapeutic drug for neurological diseases,¹¹⁰ which is converted into the neurotransmitter dopamine in the brain (Figure 6E). Dopamine itself cannot cross the blood-brain barrier, but its primary metabolite, HVA, is able to enter the peripheral bloodstream via the barrier.⁴¹ By implanting a fiber sensor into the tail vein to monitor HVA concentration in blood in real-time, changes in dopaminergic neuronal activity within the central nervous system can be indirectly reflected. Research shows that after intrahippocampal injection of levodopa in rats, dopamine concentration in the brain rapidly increases and peaks, while the rise in blood HVA concentration shows a delay of approximately 74 min (Figure 6F), and its trend matches the excitatory behavior of the animals indicated by the sensor (Figure 6G). This confirms a powerful application: indirect, real-time inference of central neurotransmitter dynamics via peripheral metabolite sensing, offering a minimally invasive, long-term strategy for studying neuropharmacology and disease mechanisms.

In summary, the use of implantable electrochemical sensing for blood pharmacokinetic monitoring represents a dual impact advancement. Clinically, it enables a fundamental shift from a “one size fits all” dosing paradigm based on population averages toward an individualized, dynamically controllable treatment process guided by continuous patient data. In research, it provides a powerful *in vivo* tool for elucidating drug metabolism pathways, interaction mechanisms, and sources of inter-individual variability, thereby holding strong potential to accelerate and refine the drug development pipeline.

5 | CHALLENGES AND OUTLOOK

Over the past few decades, advancements in materials science and device engineering have significantly promoted the development of implantable electrochemical sensors for blood monitoring, from the design of high-performance recognition elements to the construction of anti-biofouling interfaces, and from the proposal of fibrous chemical sensors to the integration of sensors with various intravascular medical devices. Direct and continuous blood monitoring holds irreplaceable value in obtaining reliable, real-time physiological and biochemical information. Whether it is the dynamic monitoring of vital signs during surgery or the precise tracking of pharmacokinetic processes, its unique clinical significance is evident. Implantable electrochemical sensors have the potential to revolutionize traditional disease management paradigms, enabling a fundamental shift from intermittent and delayed approaches to continuous and timely ones. Despite remarkable progress, implantable electrochemical sensors for blood monitoring still face a series of critical challenges on the path toward large-scale clinical translation and application (Figure 7).

- (1) Long-term biocompatibility and sensing stability. It represents two fundamental hurdles to achieving sustained monitoring and advancing its use in practical disease management. On one hand, long-term implantation places stringent demands on the biocompatibility of sensor materials. They must minimize non-specific adsorption of biological components in the long term, while also being miniaturized to reduce hemodynamic interference and avoid causing significant discomfort to the user. The potential impact of sensor implantation itself on the local microenvironment and data validity should also be considered. The presence of a foreign body within a blood vessel may trigger local inflammatory responses, alter hemodynamics, and even promote microthrombosis. These disturbances can, in turn, affect the local concentrations of metabolites, drugs, and other analytes, making it difficult for the locally measured concentrations to accurately reflect the systemic physiological state. Therefore, systematic evaluation of these potential interferences is essential for establishing the clinical validity of data obtained from implantable sensors, which requires targeted strategies at the sensor–tissue interface. Furthermore, wound care at the implantation site should not be overlooked, as this area represents a vulnerable point for infection. On the other hand, maintaining stable and accurate monitoring

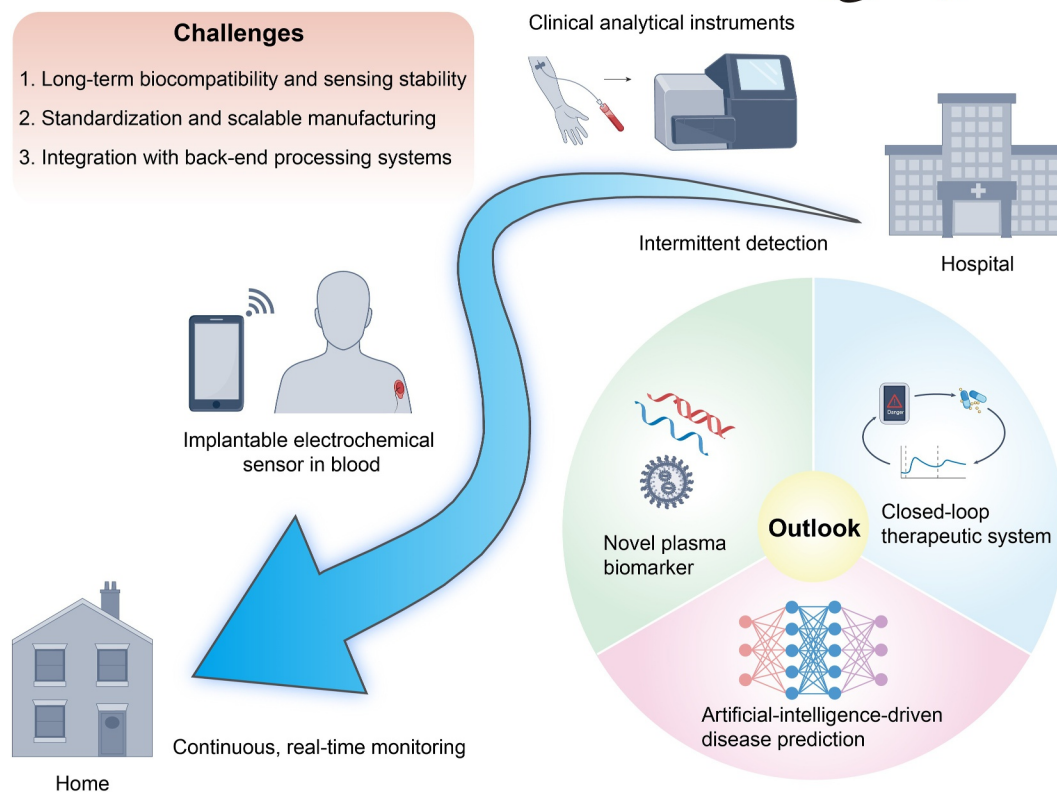


FIGURE 7 From translational challenges to future visions for implantable electrochemical sensors.

performance over extended periods remains a significant obstacle. This requires the sensing interface to resist physical erosion and chemical degradation in the complex biological environment, preventing irreversible structural or functional changes that could lead to signal drift, sensitivity loss, and ultimately unreliable long-term data.

- (2) Standardization and scalable manufacturing. Beyond achieving excellent sensing performance and biocompatibility, equal attention must be paid to inter-batch consistency and the scalable, reliable, and stable manufacturing capacity of the sensors. These aspects represent the critical practical bottlenecks that determine whether such devices can truly transition to clinical application while ensuring clinical reliability and cost-effectiveness. This demands a high degree of uniformity and process control at every stage, from sensing elements to electrode materials and encapsulation processes. Future research should systematically focus on the co-design of material synthesis, interface engineering, microfabrication processes, and quality management systems to bridge the pathway from laboratory prototypes to clinically viable products.
- (3) Integration with back-end processing systems. A critical step toward the successful clinical translation of this technology is the effective integration of the sensor with back-end system components, including signal

processing and transmission modules, data storage units, and power systems, to form a complete, stable, and clinically viable monitoring solution. Currently, most implantable electrochemical sensors adopt a “semi-implantable” architecture, where the sensing element resides in the body and is connected via external leads to signal processing and power modules outside the body. This design necessitates a strong focus on ensuring long-term stability at the sensor-module interface and secure external fixation to minimize interference with *in vivo* monitoring. Looking forward, advancing toward the development of “fully implantable systems” will significantly enhance long-term system stability and patient convenience, representing a key direction for next-generation technological evolution. The key to realizing such systems lies in overcoming challenges related to *in vivo* energy supply and data transmission. For energy, wireless power transfer (e.g., inductive coupling), implantable energy harvesting, and storage devices (e.g., biofuel cells, piezoelectric nanogenerators, metal-air batteries) have been actively explored, although they currently face limitations in energy efficiency and long-term stability. For data transmission, radio-frequency telemetry represents a highly promising approach, while near-field communication and optical methods offer alternative pathways with trade-offs in bandwidth, tissue penetration, and power

consumption. Addressing these challenges requires integrated co-design of sensing, power, and communication modules, a frontier that will benefit from advances in low-power electronics and miniaturized energy storage technologies.

Building on the progress in addressing these challenges, several promising directions await further exploration in this exciting field (Figure 7). The first lies in developing high-performance sensing systems for newly discovered blood biomarkers, which are closely linked to the early diagnosis of major diseases such as neurodegenerative disorders, cancers, and acute cardiovascular events. Combined with multi-functional integration, this could lead to the creation of implantable blood-sensing chips capable of large-scale, continuous health monitoring, paving the way for earlier disease detection and management. Secondly, the construction of closed-loop therapeutic systems based on continuous blood monitoring feedback will enable real-time, automated intervention, moving toward proactive and dynamic disease management. Finally, artificial intelligence (AI), with its powerful data-processing capabilities, offers a natural complement to implantable sensors that generate vast amounts of continuous data. By extracting deeper health insights and establishing personalized diagnostic and early-warning models, AI can help shift the medical paradigm from “diagnosis after symptom onset” to “prediction and early intervention,” truly realizing the goal of preventing disease before it occurs.

To realize these visions and overcome the existing challenges, deep convergence and collaborative innovation across disciplines such as materials science, electronic engineering, clinical medicine, and artificial intelligence are indispensable. It is only through such interdisciplinary synergy that implantable blood monitoring technology can be accelerated from the laboratory to clinical application, ultimately advancing the practical implementation of precision medicine.

AUTHOR CONTRIBUTIONS

Kuangyi Zou: Conceptualization, investigation, writing—original draft, writing—review and editing. **Yuanzhen Wang:** Writing—review and editing. **Haidong Wang:** Writing—review and editing. **Ye Zhang:** Conceptualization, funding acquisition, writing—original draft, writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data supporting the conclusions of this review are derived from previously published studies and are available in the cited references. No new data were generated or analyzed.

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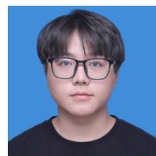
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