

Next-generation biosensing for in situ monitoring

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In situ physiological analyte measurement is pivotal for global health, yet existing in situ biosensors are commonly limited in scope. Adapting ex situ biosensors for in situ diagnostics poses challenges, including high sensitivity without pre-enrichment or pre-amplification, long-term stability in complex environments, dynamic physiological condition monitoring, and handling massive, heterogeneous datasets from various environments. In this Review, we discuss the evolution of in situ biosensing technologies, focusing on how to overcome the limitations of traditional ex situ systems through careful sensor design, encompassing innovative materials, optimized architecture and novel integration strategies. Key design components—miniaturized platforms and power supply systems—that integrate implantable, ingestible and environmental monitoring devices for real-time monitoring need to be considered along with environmental needs, data processing and analysis, and regulatory guidelines to achieve commercial and translational success of in situ biosensing.

In situ biosensing is a rapidly evolving field, driven by the growing demand for real-time, rapid and accurate biomarker detection. For example, the global wearable biosensor market, valued at US\$31.6 billion in 2024, is projected to expand at a compound annual growth rate of 7.7%, reaching US\$66.2 billion by 2034¹. While traditional ex situ biosensing remains a cornerstone of modern diagnostics—gold-standard techniques such as quantitative polymerase chain reaction and enzyme-linked immunosorbent assays² deliver high precision, reliability and flexibility—it is limited by high reagent costs and reliance on bulky, complex laboratory infrastructure. To mitigate these issues, isothermal amplification and the use of polyclonal antibodies into portable sensing platforms, including colloidal gold immunochromatographic assays³ and point-of-care testing⁴, were introduced. Although these integrated methods enhance portability and facilitate on-site diagnostics, they often suffer from reduced specificity and

sensitivity caused by non-specific amplification and variability in polyclonal antibody performance.

Since the 2010s, technological breakthroughs have accelerated the shift towards in situ biosensing (Fig. 1a). Innovations in biological and chemical sensing mechanisms, high-molecular-weight polymers, antifouling materials, micro- and nanofabrication techniques, and energy-harvesting technologies, coupled with the integration of the Internet of Things (IoT), have notably enhanced biosensor functionality^{5,6}. For example, one-step biosensing platforms now eliminate the need for sample preprocessing and target amplification, increasing efficiency and accessibility^{7,8}. In addition, hydrated interfacial polymers have been integrated to enhance antifouling performance⁹, while controlled drug-release strategies have improved the biocompatibility of implantable biosensors^{10,11}. Concurrently, IoT-enabled biosensors have transformed real-time data collection,

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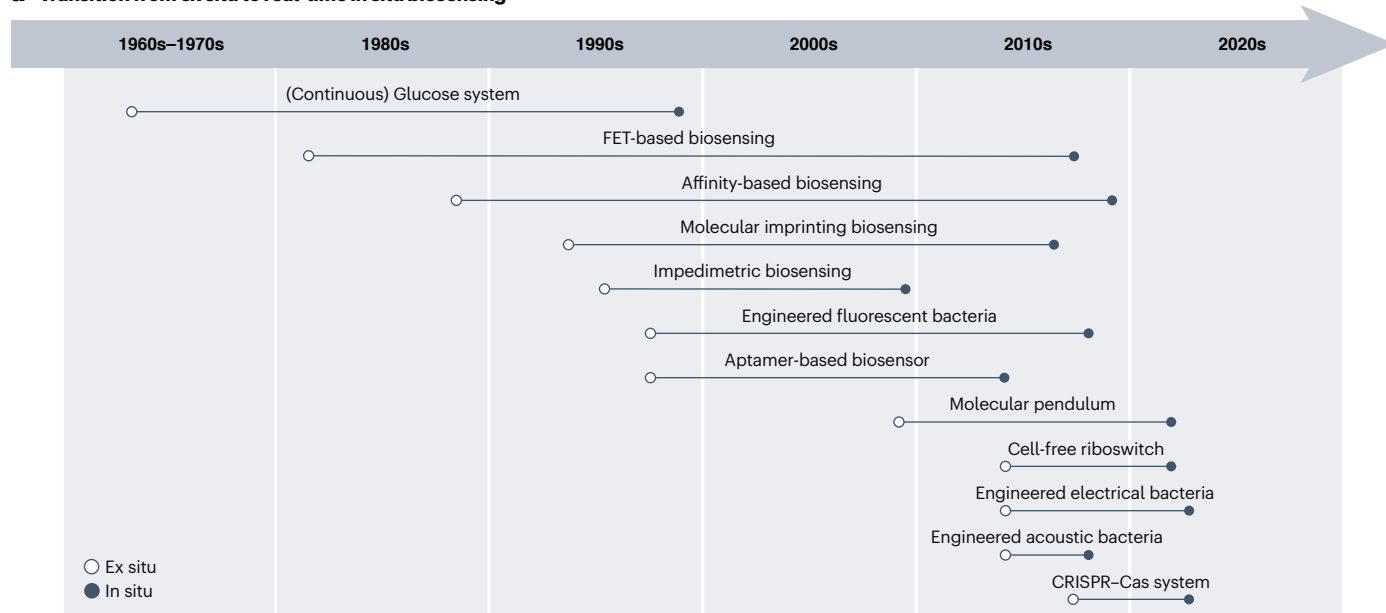
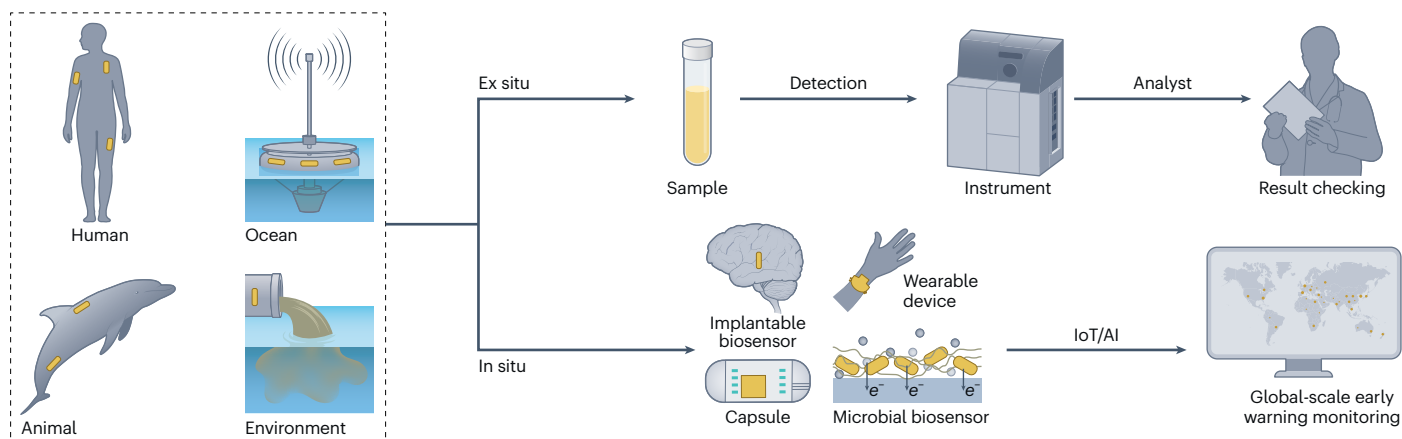
a Transition from ex situ to real-time in situ biosensing**b Comparison of ex situ and in situ biosensing techniques**

Fig. 1 | Development of in situ biosensing. **a**, Timeline of technological advances. Major milestones illustrate the transformative evolution from ex situ to in situ biosensing. In 1962, L. C. Clark Jr proposed the first enzyme-based glucose sensor for blood¹⁵⁵, which eventually led to Medtronic's launch of the first commercial continuous glucose monitoring system (MiniMed) in 1999¹⁵⁶. The development of the first FET-based enzyme biosensor in 1980¹⁵⁷ was soon followed by its application in wireless ocular diagnostics¹⁵⁸. Early protein biosensors founded on antibody-antigen recognition¹⁵⁹ evolved into long-life affinity-based in situ systems¹¹³. The initial use of network-imprinted polymers for nucleic acid binding in 1993¹⁶⁰ has progressed to real-time trypsin sensing via molecular imprinting¹⁶¹. The evolution continued from early impedimetric enzyme sensors¹⁶² to platforms that enable the real-time monitoring of bacterial growth¹⁶³. The pioneering use of fluorescent-engineered bacteria for small-molecule detection in 1998¹⁶⁴ has advanced to their deployment in health monitoring by 2018⁷². Fluorescent aptamer-based strategies transitioned from in vitro biosensing in 1998¹⁶⁵, to in vivo tracking of circulating biomarkers¹³¹.

The molecular pendulum method, initially developed for protein sensing¹⁶⁶, has been refined into a reagentless in situ approach for biomolecular analysis³⁷. The discovery of riboswitches as RNA-based sensors in bacteria¹⁶⁷ has inspired their integration into wearable devices⁵⁶. Engineered electrical bacteria, first demonstrated for biosensing in 2013¹⁶⁸, had been adapted for environmental contaminant detection by 2022⁶⁸. Engineered acoustic bacteria introduced in 2014 as ultrasound reporters⁷⁶ have been used for non-invasive imaging in mammals⁷⁷. CRISPR-based biosensing methods, initially demonstrated in the 2010s¹⁶⁹, have evolved to support long-term monitoring of universal nucleic acids⁸⁷. **b**, Ex situ versus in situ biosensing. Conventional ex situ biosensing involves multiple discrete steps, such as sample collection, processing and analysis, which often depend on extensive laboratory infrastructure. In contrast, in situ biosensing integrates these processes into a single platform, enabling real-time, on-site monitoring. When coupled with the IoT and AI, in situ biosensing can facilitate the development of global-scale warning systems, thereby enhancing diagnostic capabilities and environmental assessments.

and artificial intelligence (AI)-driven analytics have facilitated the processing of vast biosensing datasets^{12,13} (Fig. 1b). These collective advancements have expanded the real-world applicability of in situ biosensing across medical diagnostics, environmental monitoring and global health surveillance.

Despite its potential, the transition from ex situ to in situ biosensing is challenged by several hurdles: (1) the complexity associated with

multi-step preparations or reactions; (2) the frequent reduction in efficacy in complex environments caused by biofouling; (3) complications and host maladaptation arising from the foreign body response (FBR) for an implantable device in physiological conditions; (4) the constraints of sensor size that make scalability and integration difficult; (5) the reliance of multifunctional devices on municipal power sources (for example, an external supply or requiring frequent recharging),

Table 1 | Comparative analysis of major in situ biosensing modalities

Parameters	Redox enzyme-based biosensing	Reporter-labelled biosensing	Label-free biosensing	Engineered cell biosensing
Primary analyte classes	Metabolites, small molecules: glucose, lactate, uric acid, amino acids	Nucleic acids, proteins, small molecules: cytokines (IL-6, TNF), C-reactive protein, specific DNA/RNA sequences	Proteins, viruses, small molecules: SARS-CoV-2 virus, spike protein, neurotransmitters (dopamine, serotonin)	Toxins, metabolites, pathogens: heavy metals, riboflavin, oxyanions (tetrathionate, thiosulfate), haem
Biofluid/environment	ISF, blood, saliva, GI tract	ISF, blood, brain tissue	Breath (aerosols), ISF, brain tissue	GI tract, water, soil
Assay physics and mechanism	Catalytic reaction: enzyme oxidizes analyte; electron transfer generates amperometric/colorimetric signal	Binding-induced conformational change alters distance of a redox reporter (for example, methylene blue) from an electrode, modulating electron transfer	Direct measurement of electrical property change (for example, capacitance, impedance) upon target binding to an immobilized probe or site (aptamer, antibody, MIP)	A genetically encoded circuit triggers expression of a reporter protein (for example, luciferase, gas vesicles) upon analyte detection
Sample preprocessing	No (designed for direct measurement in complex media)	No (for integrated in situ formats like microneedles)	No (may use preconcentration techniques)	No (the living cell is the integrated sensor)
LOD/dynamic range (for specific cases, refer to Supplementary Table 3)	Low (nM to mM range)/narrow to moderate (about two to three orders of magnitude)	Very high sensitivity (fM to nM range)/very wide (often four to six orders of magnitude)	Moderate (nM to μ M)/moderate	Can be very high sensitivity (pM)/wide (but often sigmoidal)
Response time	Fast (seconds to minutes, enables continuous monitoring) ^{74,146}	Moderate (minutes, limited by binding kinetics) ³⁸	Fast (minutes, enables real-time monitoring) ^{86,147}	Slow (hours, limited by gene expression and protein synthesis) ^{5,72}
Operational stability	High (weeks to months, demonstrated in commercial devices) ^{146,148}	Moderate (days to weeks, depends on bioreceptor and electrode stability) ³⁴	High (solid-state sensors such as FETs can be very stable) ¹⁴⁹	Low to moderate (limited by cellular viability and genetic circuit stability in complex environments) ⁷³
Key strength	Maturity, reliability and commercial deployment for continuous metabolite monitoring	Extremely high specificity and sensitivity for a wide range of non-metabolite targets	Real-time, direct measurement of binding events without secondary labels	Low-cost, self-replicating, capable of detecting complex stimuli and operating in harsh environments
Key limitation	Requires frequent recalibration; limited to analytes with known enzymes	The need for a synthetic redox reporter adds complexity	Can be susceptible to non-specific binding (fouling), which must be managed	Slow response time and challenges in maintaining consistent cell viability and function in situ
Power source	Small batteries (lithium coin cell) or integrated energy harvesting (for example, perovskite solar cell) ^{146,150}	Typically requires a potentiostat or small battery for readout ^{36,38}	Low. Can be passive (FETs) or use near-field communication for wireless power ⁸⁶	Low (cells are self-powered). Readout electronics (photodetector, radio) require a battery ^{72,73}
Miniaturization and integration	High: integrated into microneedles, contact lenses, mouthguards, subcutaneous implants ^{14,151,152}	High: integrated into microneedle arrays, wearable microfluidics, implantable microelectrodes ^{36,38,153}	High: integrated into wearable masks, implantable neuroprobes (Si based), ingestible capsules ^{85,149,154}	Moderate: integrated into ingestible capsules with bacterial chambers, environmental probes ^{72,73}
Representative use cases	Commercial continuous glucose monitor (for example, FreeStyle Libre), wearable lactate patches, ingestible glucose capsule ^{14,74}	In vivo nucleic acid detection, implantable cytokine (IL-6/TNF) monitors, brain dopamine sensing ^{38,48,153}	Wireless breathalyser for SARS-CoV-2, implantable brain serotonin microchips ^{85,149}	Ingestible capsule for GI bleeding (haem detection), environmental monitoring of water/soil toxins ^{6,72}

This table offers a concise comparison of four leading in situ biosensing technologies, highlighting their core principles, performance and applicability. It contrasts critical parameters such as target analytes, sensitivity, response time, stability and miniaturization potential. The analysis reveals trade-offs: enzyme-based sensors are mature and fast but target a limited range of metabolites, while reporter-labelled methods offer exceptional sensitivity at the cost of added complexity. Label-free platforms enable real-time monitoring but face fouling challenges, and engineered cell sensors are versatile and self-powered but suffer from slow response times. This table serves as a practical guide for selecting the appropriate sensing modality based on the specific requirements of the target analyte, environment and desired operational characteristics.

which might not be sustainable for long-term in situ applications in remote or resource-limited settings; (6) the considerable gap between the collection and analysis of mass data from multi-scenario biosensing; and (7) the intrinsic variability of in situ environments. Unlike ex situ measurements, in situ systems are continuously exposed to physical (for example, temperature shifts, motion), chemical (for example, pH or ionic fluctuations) and biological (for example, enzymatic activity, immune responses, microbiota interactions) changes, all of which can compromise biosensor performance. Effectively addressing

these challenges is essential for successfully implementing in situ biosensing technologies.

In this Review, we examine the field of in situ biosensing, covering its fundamental principles, current challenges and future directions. We analyse key enabling technologies, including sensing platforms, antifouling strategies, biocompatibility enhancement methods and energy solutions for long-term operation, while highlighting the transformative impact of IoT and AI integration. We further explore critical applications in global health monitoring and conclude by discussing

emerging opportunities to highlight the potential of in situ biosensing to revolutionize analytical sensing across multiple areas.

Strategies for advancing ex situ to in situ biosensing

In situ biosensing platforms have extensively advanced analytical methods for the real-time monitoring of biomolecules within biological environments. Unlike traditional ex situ methodologies that require sample collection, transport and subsequent analysis in laboratory settings, in situ platforms improve the temporal resolution and contextual relevance of biosensing, providing more immediate and applicable insights into biological processes. Each type of in situ sensing platform has evolved considerably, transitioning from ex situ applications to in situ implementations, thereby enhancing sensitivity, specificity and overall diagnostic capabilities (Table 1).

Redox enzyme-based biosensing

Redox enzyme-based biosensing functions by leveraging the catalytic activity of enzymes such as glucose oxidase (GOx), amino acid oxidase, lactate oxidase and hydroxybutyrate dehydrogenase (Fig. 2a). When the target molecule (substrate) approaches the enzyme's active site, it undergoes a specific oxidation or reduction reaction that involves the transfer of electrons to an electrode surface, generating a measurable electrochemical signal (for example, current) proportional to the target concentration¹⁴. It has emerged as one of the most mature methods for in situ detection within electrochemical sensor frameworks. Numerous companies have developed and commercialized products that utilize this method for glucose monitoring (such as Abbott with its FreeStyle Libre 3 system, Medtronic's Guardian Sensor 3 and Dexcom G6)^{15,16}. Enhanced performance relies on covalent immobilization of the enzyme onto the electrode surface via bonds formed with specific amino acid side chains (for example, lysine- ϵ -amino, histidine-imidazole, cysteine-thiol, aspartic/glutamic acid-carboxyl bonds)^{17,18}. Furthermore, encapsulation strategies using biopolymers such as chitosan and bovine serum albumin serve as efficient alternatives, preserving enzymatic activity and providing a protective barrier in complex environments¹⁹. Such immobilization not only preserves the enzyme's catalytic activity but also stabilizes it in biological fluids, easing controlled enzymatic reactions and improving the overall efficiency of the sensing system.

Despite the benefits of in situ biosensing, environmental factors (for example, temperature and pH) can decrease the stability of redox enzymes and the accuracy of measurement. To enable reliable in situ function, researchers are progressively utilizing biocompatible substances²⁰ to enclose enzymes and electrodes, thereby intensifying their robustness against environmental fluctuations. For example, a magnetic nucleic acid polymer synthesized based on a self-assembly

programmable method has been used for enzyme encapsulation²¹, which provides the undisturbed separation of the enzyme from the reaction medium and distinctly enhances both the reusability and stability of in situ platforms, particularly when measuring low-level targets such as glucose. These protective materials help keep the function of GOx during real-time monitoring, guaranteeing efficient substrate diffusion and product formation²². Further enhancements in sensor sensitivity are still needed to achieve reliable performance across diverse biological environments.

Notable endeavours have focused on optimizing modifications of electrode surfaces to enhance the performance of in situ redox enzyme biosensors. Incorporating nanomaterials (for example, gold nanoparticles, graphene oxide, carbon nanotubes or quantum dots) and conductive polymers (for example, polythiophene, polyethyleneimine, polypyrrole or polyaniline)²³ has increased both the direct binding capability as well as the efficiency of electron transfer between the electrode interface and the enzyme²⁴. For example, a conductive organic polymer-based biosensor conjugating with acetylcholinesterase for the detection of organophosphorus. This strategy achieved remarkable catalytic efficiency, with detection limits of 1.5×10^{-13} g ml⁻¹ for methyl parathion and 3.4×10^{-14} g ml⁻¹ for paraoxon²⁵. In addition, integrating colorimetric techniques into in situ sensor designs (for example, glucose and lactate)^{26,27} provides alternative approaches for real-time measurement. Combining these approaches notably improves the performance and expands the potential applications of redox enzyme biosensors, making them well suited for monitoring critical biological processes and environmental changes.

Redox-labelled electrochemical biosensing

Redox-labelled biosensing uses redox-active labels or probes (for example, ferrocene, methylene blue or oxidoreductase)²⁸ attached to recognition elements (for example, antibodies, aptamers or nucleic acids). Target binding induces conformational change or brings the redox label into proximity with the electrode surface, modulating the label's electrochemical behaviour (for example, alters electron-transfer efficiency) and producing measurable signal changes (current or voltage). This technique has evolved from classical ex situ methods to more robust in situ approaches. While traditionally employed ex situ for controlled measurements of antigen-antibody or nucleic acid interactions, this approach initially suffered from limited target diversity. High-throughput aptamer screening has since expanded its scope, enabling multiplexed detection of small molecules (such as phenylalanine²⁹ and doxorubicin³⁰) and proteins (for example, vascular endothelial growth factor and neutrophil gelatinase-associated lipocalin)^{31,32}, via in situ redox-label biosensing platforms. The transition to in situ platforms capitalizes on direct binding to deliver precise electrochemical readouts reflecting molecular interactions in real time. Nevertheless,

Fig. 2 | In situ biosensing mechanisms. **a**, Redox enzyme-based biosensing. Redox enzyme-based biosensors oxidize various substrates (for example, glucose, amino acids and lactic acid) and transfer electrons to electrodes, thereby producing electrical signals or reducing chromogenic substrates for colorimetric detection (for example, glucose oxidase integrated with a potassium iodide (KI)-iodine (I₂) starch system). **b**, Reporter-labelled electrochemical biosensing. Electrochemical sensors use hairpin structures or a target-induced strand-displacement strategy for biosensing. Detection depends on distance changes between the probe and the electrodes (strand-displacement strategies and aptamer-based biosensors) or hydrodynamic alterations (molecular pendulum method) that occur upon target binding. **c**, Label-free electrochemical biosensing. Molecular imprinting uses specialized conductive polymers that selectively bind analytes, enabling detection via resultant changes in electrical signals. Affinity-based immunoassay and aptamer-binding biosensing directly detect proteins and small molecules through specific binding interactions. Nucleic acid diagnosis can also be achieved via Ago- or Cas-mediated binding. **d**, Cell-free riboswitches bind targets,

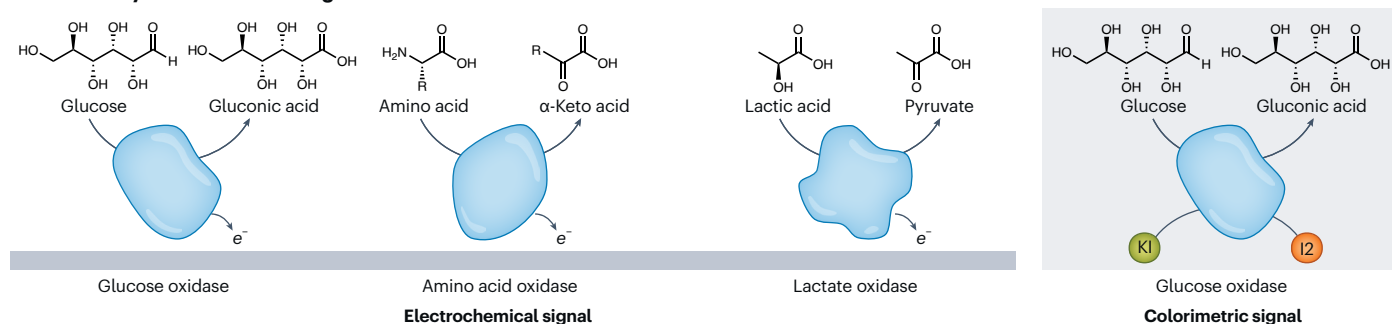
undergoing conformational changes that trigger the expression of fluorescent reporter proteins. Similarly, CRISPR-Cas systems bind targets to activate Cas-mediated *trans*-cleavage (for example, to cleave a nucleic acid probe labelled with a fluorophore (F) and a quencher (Q)), generating a fluorescence signal. **e**, Fluorescently engineered cells continuously express reporter proteins (for example, from a recombinant genes (Rec)-fluorescent protein (FP) gene fusion construct) that are monitored in the presence of target analytes. Ultrasound-enabled cells express acoustic reporter genes (ARGs) that encode for gas vesicles in response upon target detection, when biomarker binding to a membrane sensor kinase triggers phosphorylation of a cytoplasmic response regulator (RR) that activates transcription of ARGs from a specific promoter¹⁷⁰. Electricity-producing cells utilize cytochrome proteins (for example, sulfide-quinone reductase (SQR)) to shuttle electrons generated by substrate oxidation from the cytoplasm (for example, nicotinamide adenine dinucleotide phosphate (NADPH)) to an electrode⁶⁸. Panel e adapted with permission from: ref. 170 (ultrasound-enabled cells) under a Creative Commons licence [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/); ref. 68 (electricity-producing cells), Springer Nature Limited.

several issues such as relatively high background noise still endure, presenting the commitment to further advancement of monitoring in situ platforms (Fig. 2b).

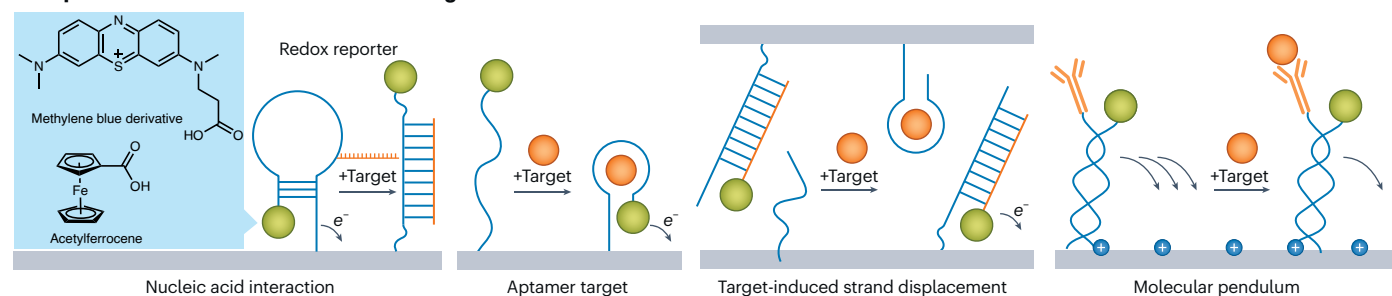
To address these issues, target-induced strand-displacement techniques that release the redox probes from the recognition area to the detection area have been developed, thereby minimizing background

noise and boosting sensitivity. One such strategy exploits a hairpin DNA aptamer containing both a specific target binding site and a redox reporter. In the absence of the target, the hairpin remains locked, producing only blank signals. When the target is introduced, the aptamer opens to recognize complementary nucleic acids on the sensor surface, sparking a strand displacement reaction that conveys the redox probe

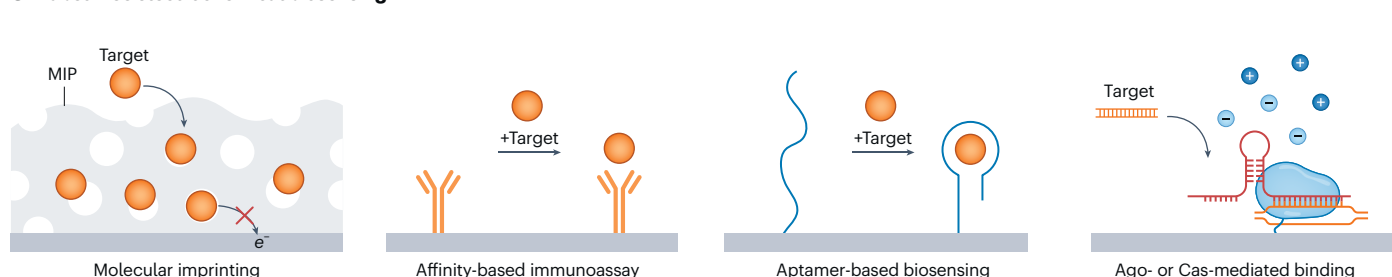
a Redox enzyme-based biosensing



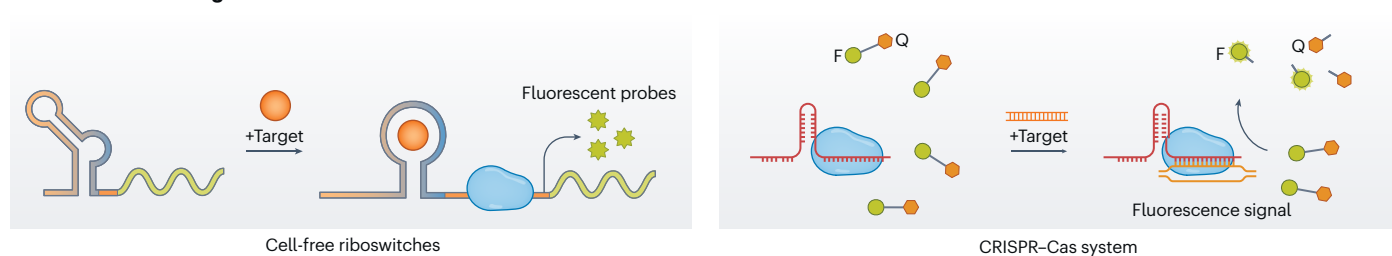
b Reporter-labelled electrochemical biosensing



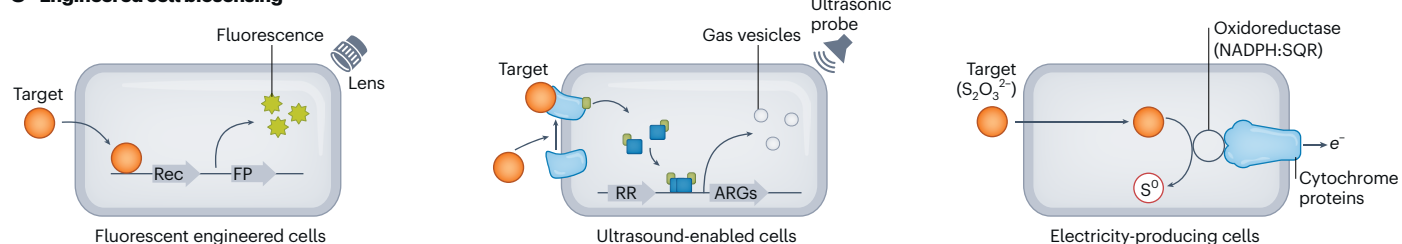
c Label-free electrochemical biosensing



d Cell-free biosensing



e Engineered cell biosensing



and generates noticeable electrochemical signals. This approach has achieved a low detection limit of 5 nM for ATP³³. Despite these progresses, sensitivity issues remain, particularly under in situ conditions without target amplification or sample enrichment. To further upgrade sensitivity, researchers have integrated nanomaterials and conductive polymers into biosensing platforms^{34,35}. For example, integrating gold nanoparticles distinctly enhances the conductivity and surface area of sensors, developing more efficient redox reactions and reaching an ultralow limit of detection of 0.14 pM for oestradiol³⁶. These advancements facilitate the transition from ex situ to in situ biosensing by enabling the monitoring of targets with higher sensitivity and reduced background interference.

The molecular pendulum method represents an advanced approach: target binding alters the Brownian motion or field-induced transport of a tethered redox reporter molecule near the electrode³⁷. Measuring this transport variation provides a highly sensitive, reagent-free signal transduction mechanism. By erasing the demand for further reagents, it distinctly decreases both the time and costs of target analysis and has established exceptional efficiency in measuring cancer and inflammatory biomarkers. However, this approach requires acceptable in vivo verification in complicated physiological situations and suffers from slow dissociation kinetics of high-affinity receptors, which prevents real-time tracking of decreasing analyte concentrations. To overcome these challenges, an active-reset in situ protein biosensor uses high-frequency electrical oscillations to forcibly dissociate the bound target molecule, enabling the sensor to return to its unbound state within 1 minute for continuous monitoring³⁸. This method enhances both the sensitivity and accuracy of the active-reset protein detection system, facilitating in vivo measurement of inflammation biomarkers (for example, interleukin-6 (IL-6) and tumour necrosis factor (TNF)) in interstitial fluid (ISF) for durations exceeding 350 minutes. These innovations represent an important breakthrough, paving the way for truly real-time protein-sensing capabilities that deepen our understanding of complex biochemical phenomena (that is, antibody–antigen interaction and pattern recognition receptors) in live systems.

Label-free electrochemical biosensing

Label-free biosensing has accelerated conspicuously beyond conventional ex situ techniques. By eradicating the requirement for fluorescent, electrochemical or other labelling probes that can complicate bioanalysis³⁹, this approach is capable of directly monitoring biological and chemical molecular interactions that occur when a target molecule binds to a surface-immobilized recognition element (for example, antibody, aptamer, imprinted polymer). The advancement towards in situ biosensing systems is driven by ingenious sensor technologies, for example, field-effect transistors (FETs) that use the intrinsic properties (for example, highly sensitive to surface charge) and high specific interactions of targets. Collectively, label-free biosensing platforms provide real-time monitoring capabilities essential for elucidating disease mechanisms and deciphering dynamic biological processes within their native environments (Fig. 2c).

Among the most forthright approaches, molecular imprinting has brought appreciable consideration for its ability to achieve bespoke binding sites tailored to specific targets. Its fundamental low immunogenicity and cost-effectiveness cause molecular imprinting that is particularly suitable for real-time monitoring of a broad array of targets, including electrolytes (for example, Na⁺)⁴⁰, small molecules (for example, leucine, isoleucine and valine)⁴¹, proteins (for example, IL-1 β)⁴² and viruses (for example, lentivirus)⁴³. A molecularly imprinted wearable biosensor that incorporates a sweat extraction module with paper-based microfluidics has been demonstrated for continuous monitoring of sweat parameters, including volume, secretion rate, Na⁺ concentration and cortisol levels⁴⁰. Notwithstanding these advantages, molecular imprinting can suffer from lower specificity relative to other label-free modalities. To address this limitation, direct recognition

strategies such as affinity-based immunoassays or aptamer-based biosensing provide high-affinity binding^{44,45}. Aptamers offer excellent selectivity for small molecules such as dopamine, serotonin and glucose⁴⁶. When integrated with nanomaterials or FETs, these sensors exhibit markedly enhanced sensitivity, as illustrated by a wearable aptamer–FET platform for cortisol monitoring that achieved a detection limit of 1 pM (ref. 47).

Despite these improvements, numerous label-free biosensing approaches have essentially concentrated on tracking and detecting proteins or small molecules. To expand the capacity of in situ label-free biosensing detection to nucleic acids, methods utilizing argonaute (Ago) or CRISPR-associated (Cas) proteins can be modified on substrates such as sensor interfaces. For instance, an Ago-based wearable system enables stable detection of ultratrace, unamplified nucleic acids in vivo up to 14 days⁴⁸. Integrating these contemporary techniques allows label-free biosensing systems to transition effectively from ex situ to in situ utilizations, thereby advancing sensitivity, specificity and versatility in measuring a broad spectrum of targets within their native environments.

Cell-free biosensing

Cell-free biosensing encircles a suite of analytical approaches that leverage isolated biological components (for example, enzymes, proteins and nucleic acids) without living cells to measure or quantify specific targets, including metal ions, antibiotics and nucleic acids⁴⁹. By tackling the intrinsic biorecognition capabilities of these components, cell-free biosensing systems provide streamlined procedures that are particularly well suited for utilizations in environmental monitoring, clinical diagnostics and bioprocess monitoring⁵⁰ (Fig. 2d). A distinguished case of cell-free biosensing associates RNA-based switches, such as toehold switches and riboswitches, which experience conformational changes upon target binding. These switch-based molecular biosensors can measure a wide array of targets, including small molecules (for example, tetracycline, dopamine and thyroxine)^{51,52}, nucleic acids (for example, pathogen genomes and messenger RNA)^{53,54} and proteins (for example, phage MS2 coat protein, C-reactive protein and human IL-32 γ)⁵⁵. For example, a wearable, freeze-dried cell-free riboswitch biosensor⁵⁶ has been manifested for the detection of theophylline and Ebola RNA, accentuating the capability of engineered riboswitches to analyse multiple biomarkers (including viral components and antibiotics) and thereby heighten rapid diagnostic applications⁵⁷.

Although switch-based biosensors have proven to be powerful, their sensitivity endures a demanding limitation, particularly in measuring low-abundance biomolecules amid complex biological systems where native environmental intervention can bargain signal loyalty. To address these challenges, recent progress has incorporated the CRISPR–Cas technique into wearable biosensing platforms. These innovative platforms leverage the collateral cleavage activity of Cas enzymes upon target binding and benefit from excellent programmability^{58,59}. As a result, the integration of the CRISPR–Cas system has dramatically enhanced sensitivity, achieving detection limits in the attomolar range⁶⁰. For example, a CRISPR–Cas12a-based toehold sensor has been demonstrated to measure as few as 100 copies of the entire genome of a model *Salmonella* pathogenic cell, epitomizing the transformative developments in cell-free biosensing⁶¹.

Despite their achievements, both riboswitch- and CRISPR-based cell-free biosensing approaches have been designed predominantly for ex situ biosensing applications, limiting their applications for continuous in situ monitoring. Recent advances in wearable technology have begun to address this gap by enabling in situ pathogen diagnosis. For example, flexible substrates and textiles integrated with freeze-dried circuits⁵⁶ facilitate non-invasive viral diagnosis within 90 minutes under real-world environments. These advancements not only deepen our understanding of pathogen dynamics but also boost diagnostic accuracy and enable prompt early medical intervention. Moreover, by

integrating cell-free biosensing with emerging materials and electronics (for example, digestible electronics, electronic textiles and flexible microfluidics)^{62,63}, the potential for in situ monitoring in clinical medicine and environmental settings is steadily increasing.

Engineered cell biosensing

By integrating sensing gene clusters, engineered microbial cells can be transformed into in situ biosensors, enabling them to recognize specific targets, process biological information and transmit results across various environments⁶⁴. Microbial whole-cell biosensors (MWBs) serve as an advanced set of in situ biosensing tools that use engineered microbial cells to generate measurable signals, such as fluorescence, acoustic and electrical signals (Fig. 2e), for the measurement and quantification of various analytes. These analytes contain heavy metals (for example, mercury or zinc)⁶⁵, organic acids (for example, acetate)⁶⁶, carbohydrates (for example, urine glucose)⁶⁷, oxyanions (for example, thiosulfate)⁶⁸, aromatic molecules (for example, quinones or pyocyanin)⁶⁹ and biocides (for example, herbicide dicamba)⁷⁰. Unlike other in situ biosensors that use redox reporters, redox enzymes, label-free biosensing and cell-free systems, MWBs with self-replication and self-repair capabilities can decrease production costs and expand their operational lifespan, making them particularly suited for complex conditions. Among the various MWBs, those producing fluorescence outputs are widely used, providing visual results for sensing targets. The extensive application of engineered cells dependent on fluorescence and bioluminescence for measuring heavy metals, toxins and organic pollutants has been thoroughly reviewed in past literature⁷¹.

Current advances in ingestible electronic platforms have enabled in situ tools of fluorescent-engineered microbial cells for administering gastrointestinal (GI) disorder diseases such as inflammatory bowel disease and irritable bowel syndrome. These advances expedite precision personalized treatment strategies by leveraging real-time gut health information. For instance, an ingestible micro-bio-electronic device (IMBED)⁷² was developed to measure GI bleeding by integrating environmentally robust bacteria within a miniaturized electronic device that wirelessly transmits diagnostic results in a porcine model. Later, an updated version of IMBED was designed for sensing labile inflammatory targets⁷³, although its requirement for surgical placement within the small intestine restricts its clinical applications. To address these constraints, a self-powered ingestible wireless biosensing capsule with special coatings has been engineered to non-invasively monitor GI metabolites⁷⁴. This design incorporates a pH-responsive enteric coating that temporarily protects the capsule from the acidic environment of the stomach and subsequently dissolves in the pH-neutral intestinal medium, while silicone/polyurethane coatings provide insulation for the electronic components, ensuring their functionality throughout the digestive process. Acoustic signals afford noticeable advantages over fluorescent signal outputs for precise target localization. Although ultrasound-based imaging has been broadly employed clinically, its utilization at the cellular level has been hindered by the lack of appropriate intracellular probes⁷⁵. Recent studies into microbial buoyancy regulation have yielded several nanostructure gas vesicles as contemporary intracellular ultrasonic reporters. These nanostructures produce robust, durable ultrasonic signals and, when functionally expressed in cells, enable bioimaging at the cellular level—an excellent capability previously unattainable⁷⁶. Furthermore, the successful integration of the gas vesicle gene into microorganisms and mammalian cells effectively transforms these cells into intrinsic ultrasonic biosensors^{77,78}. This approach aids real-time imaging with high spatial resolutions below 100 μm , making it feasible to visualize tumour cells in vivo. Despite their encouraging achievement, further refinements are required to increase the quantitative power of these ultrasonic MWBs. As eminent in situ probes, ongoing inspections are essential to completely explicate and optimize their traits for biomedical applications.

Designing MWBs for real-time monitoring in complex environments, such as sewage systems, necessitates interference-free signal acquisition and rapid response times⁷⁹. Electrical signal modality provides recognizable advantages over fluorescent and acoustic transductions by enabling direct measurement in opaque conditions and accelerating target quantification. These advantages make electrical biosensors particularly suitable for integration with electronic devices for utilizations ranging from wastewater treatment to intestinal monitoring. For example, the electroactive *Shewanella oneidensis*, which is well known owing to its extracellular electron-transfer capability, has been strapped to fabricate electricity-producing MWBs for riboflavin detection⁸⁰. Moreover, synthetic biology approaches have been used to integrate an eight-component synthetic electron transport module into bacterial hosts, *Escherichia coli*, yielding in situ biosensors that respond to specific targets, such as thiosulfate, in urban contaminate water within 3 minutes⁶⁸. This miniaturized, low-power bioelectronic MWB platform thus provides a promising tool for measuring a broad spectrum of environmental chemicals.

The choice among these technological paths depends heavily on the application. Gas vesicle-based sensors, for instance, are uniquely suited for deep-tissue in vivo imaging because ultrasound waves can penetrate opaque biological tissue. This ability to function non-invasively inside a living body comes at the cost of slower kinetics. In contrast, electronic microbe interfaces are ideal for ex vivo or environmental sensing. They can be safely integrated into devices, offer faster electrical readouts, and have excellent limits of detection and superior biocontainment. This makes them perfect for field-deployable chemical monitoring (Supplementary Table 1).

Integrated system architectures for robust in situ biosensing

The architecture and integration of in situ biosensors constitute a foundational framework enabling real-time, accurate biochemical monitoring directly within real environments. This design integrates sample collection, preprocessing, signal transduction and embedded data handling into a cohesive system, overcoming inherent challenges posed by complex chemical and biological matrices. Through synergistic microfluidics, advanced materials and precise hardware configuration, the in situ biosensors achieve the high sensitivity with long-term stability required for effective healthcare and environmental applications. A modular yet integrated architecture ensures harmonious operation across functional units, from sampling to signal processing, optimizing performance under in vivo or real-time in situ conditions (Table 1).

Sample collection and enrichment

Effective sample collection and enrichment are pivotal for the accuracy and reliability of real-time in situ biosensors. Strategic sampling methodologies must account for physicochemical properties of the sample matrix, spatiotemporal analyte heterogeneity and potential environmental interferences to ensure precise target quantification. Advanced sampling techniques, including microfluidics, iontophoresis, passive diffusion (for example, hydrogel wicking) and active pumping systems, can be leveraged to capture representative samples (for example, sweat, ISF, breath) while mitigating contamination and preserving labile biomolecules.

Continuous sample collection and transport are essential for real-time operation. Microfluidics are the primary sampling techniques used for sample acquisition owing to several inherent advantages. (1) Minimal sample volume: the handling and analysis of microlitre-to-nanolitre volumes of biofluids (for example, sweat, ISF and tear) are often available in very small quantities⁸¹. (2) Controlled fluid manipulation: the precise control over fluid dynamics (for example, flow, mixing and separation) for tasks such as timed sampling, reagent integration and filtration have been easily achieved to address conventional methods' drawbacks⁸². (3) Miniaturization: it allows for the development of

compact, portable and self-contained wearable systems that achieve sample collection, preparation and sensing on a single chip. (4) High efficiency and reproducibility: it enhances analysis reproducibility and can improve the sensitivity by pre-concentrating analytes or reducing background interference⁸³. These properties establish microfluidics as a key tool for the sampling and enrichment of in situ biosensing applications. In sweat collection, microfluidic active transport utilizes capillary forces (hydrophilic coatings) or negative pressure to directionally channel secretions, minimizing evaporative loss and environmental interference; integrated capillary-bursting valves enable temporal segmentation for dynamic pharmacokinetic profiling, while concurrent flow rate sensing via embedded electrodes ensures high spatiotemporal resolution. To counter natural intermittency, integrated iontophoresis with cholinergic stimulation (for example, carbachol) sustains secretion for days, although compositional variances (for example, elevated K^+) necessitate calibration. For instance, a skin-interfaced wearable aptamer nanobiosensor achieved a limit of detection (LOD) of 0.14 pM in non-invasive oestradiol monitoring by coupling autonomous sweat induction (iontophoresis) with microfluidic capillary-bursting valves. This ensured precise volumetric sampling (nanolitre to microlitre scale), minimized analyte dilution and evaporation, and enhanced signal-to-noise ratios³⁶. Moreover, the use of hydrophilic materials (such as layers of hydrogel or porous materials) can absorb sweat from the skin for subsequent routing into the analysis area⁸⁴; while gravity-driven collection platforms (for example, patches on the back) employing gravity help in moving sweat through the microfluidic chip network⁸⁵. For exhaled breath condensate (EBC), the pathogenic infection diagnosis system uses bionic microfluidics with bioinspired geometry (9 inlets, 7 mm outlet length, 1 mm width) and hydrophobic polydimethylsiloxane walls to trap exhaled viral aerosols via optimized fluid dynamics (~ 8 Pa pressure), while its air–liquid interface exploits the hydrophilic structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to dissolve and enrich virions directly into a microlitre-scale phosphate buffer saline reservoir. This preconcentration mechanism minimizes sample loss and delivers localized viral targets to a sensing surface, achieving rapid, amplification-free detection of virions at subpicogram per millilitre levels (LOD 1 fg ml⁻¹ for spike protein, 0.5 pg ml⁻¹ for live virus)⁸⁶.

Sample enrichment further guarantees the high sensitivity of in situ biosensors and often uses techniques similar to those used in sample collection. For ISF sampling, microneedle arrays penetrate the epidermis to access analytes continuously, while reverse iontophoresis enriches target molecules (for example, nucleic acids) via electroosmotic flow under low-current fields⁴⁸. For instance, to address the intrinsic limitation of ultratrace nucleic acid concentrations in ISF, reverse iontophoresis (10 V) has been integrated into the flexible circuit, enabling in situ electrokinetic preconcentration of negatively charged nucleic acids (for example, cell-free DNA and RNA) biomarkers towards the microneedle sensing interface, effectively pushing detection limits to subfemtomolar levels (0.3–1.2 fM)^{48,87}. Analogously, breath analysis leverages condensation traps (for example, chilled impingers) to concentrate volatile organic compounds and selective adsorbents (for example, metal–organic frameworks) to isolate low-abundance biomarkers (for example, alcohol or acetone for metabolic or health monitoring), extracting molecular information for health assessment. The EBCare wearable biosensor exemplifies this integrated strategy by combining hydrogel evaporative cooling with metamaterial radiative cooling to continuously condense exhaled vapour at high rates ($\sim 4 \mu\text{l min}^{-1}$) and bioinspired microfluidics (gradient micropillar arrays, hydrophilic channels) for rapid (< 5 minutes), gravity-independent transport, thus enriching trace biomarkers across diverse environments⁸⁵. In addition, polymeric wicking pads can also collect and enrich respiratory droplets and aerosol samples, enhancing the sensitivity of virus detection⁵⁶. These physical enrichment techniques

enable rapid and selective analyte concentration while avoiding the complexities of biological receptor engineering.

Following sampling, on-site interference exclusion can decrease the background interference, enhancing the signal by purifying the target analytes and eliminating non-specific biological matrices. Integrating sample filtration membranes directly onto sensing devices provides a simple, rigorous and effective solution. For instance, sample filtration and protection are implemented via semi-permeable membranes (0.4 μm pore size) that exclude host cells and microbiota while permitting analyte diffusion, coupled with enteric polymer coatings (Eudragit L100-55) that shield sensors from gastric degradation, enabling detection of labile biomarkers (for example, haem, nitric oxide and hydrogen peroxide) within complex GI milieus^{72,73}. Unlike traditional anti-biofouling coatings, this physical filtration approach enhances sample fidelity and signal without chemical modifications. To enhance the realism of multi-fluid biosensing (for example, breath, sweat, tears, ISF), hardware and algorithmic strategies could be integrated to mitigate the errors and interferences associated with each fluid type (Supplementary Table 2).

Signal enhancement through engineered materials and ratiometric hardware

Mechanical and electronic failures (for example, repeated mechanical stress and the finite lifetimes of electronic components) and degradation of functional component materials cause signal loss or failure of wearable and implantable in situ biosensors^{88,89}. Signal-enhanced architectures improve both the generation and the fidelity of the transduced signals within intricate biological environments through innovations in material design, signal acquisition and embedded processing^{20,90}. Two primary strategies to achieve this signal enhancement are the engineering of advanced materials and the implementation of hardware-based signal conditioning integrated within the system architecture.

Engineered materials (for example, materials for electrodes) enhance spatiotemporally controlled and selective molecular recognition, thereby directly enhancing signal specificity and sensitivity^{91,92}. For example, core–shell nanoparticles with molecularly imprinted polymer (MIP) shells provide selective binding cavities for target analytes (for example, amino acids, drugs), while a redox-active nickel hexacyanoferrate (NiHCF) core ensures stable electrochemical signal transduction. This architecture leverages the high surface-to-volume ratio of nanostructures to maximize receptor density and facilitates electron-transfer efficiency, thereby amplifying the signal response per binding event. Crucially, the exceptional electrochemical stability of NiHCF, attributed to its zero-strain ion intercalation properties, maintains signal integrity during prolonged operation in biological fluids, preventing the sensitivity drift common in conventional redox probes⁹³. Complementarily, hierarchical nano–bio interfaces inspired by biological systems (for example, intestinal mucosa) integrate nanoporous gold electrodes modified with hyperbranched polyethylene glycol (PEG) coatings and conformation-switching aptamers (named SENSBIT)⁹⁴. The nanoporous gold mimics microvilli, offering a three-dimensional bicontinuous structure that enhances both the effective surface area for probe immobilization and mass transport of small molecules. The PEG coating acts as a size-exclusion barrier, minimizing non-specific adsorption of interferents (for example, proteins, cells) while permitting analyte diffusion to embedded aptamers. This dual design preserves the binding kinetics and conformational freedom of receptors, ensuring rapid, reversible target capture and high signal gain. Furthermore, inkjet printing of optimized nanoparticle inks enables scalable fabrication of sensor arrays with minimal inter-sensor variability, ensuring consistent sensitivity across devices. Together, these material innovations, molecular imprinting for specificity, nanostructured redox materials for signal amplification and biomimetic antifouling interfaces for stability, synergistically overcome traditional trade-offs between sensitivity, selectivity and longevity, establishing a

robust foundation for next-generation biosensors. Despite these innovations, limitations persist: SENSBIT's size-exclusion blocks analytes >1 kDa, while MIPs face diffusion barriers for larger biomolecules such as proteins. Unquantified binding kinetics might also compromise temporal resolution, highlighting the need for designs balancing permeability, rapid dynamics and manufacturability.

Alongside material-based improvements, hardware-based signal conditioning uses dual- or multi-channel ratiometric architectures to compensate for environmental perturbations and reduce noise during signal readout⁹⁵. For example, the multimodal calibration architecture enhances environmental robustness in wearable hormone monitoring by integrating a multi-channel sensing system that simultaneously measures the target analyte, oestradiol and key contextual variables (pH, temperature, ionic strength) within a microfluidic reservoir. Real-time correction is achieved by dynamically calibrating oestradiol signals against these auxiliary data streams to account for pH-dependent aptamer-binding variations, ionic strength-induced drift and temperature-related kinetic effects. Embedded electronics fuse these multivariate inputs to produce context-adjusted hormone concentrations, leveraging physiologically relevant calibration parameters to maintain reliable performance in complex, dynamic sweat matrices³⁶. Similarly, the EBCare wearable biosensor integrates potentiometric (pH, NH₄⁺) and resistive (temperature) sensors to continuously monitor EBC matrix properties, enhancing the accuracy in low-ionic-strength EBC while preserving sensitivity to target analytes such as NO₂⁻ and alcohol⁸⁵. These auxiliary measurements are integrated in on-chip analogue circuits that dynamically adjust the baseline biosensor response in real time, offering a comprehensive framework for precise biomarker sensing in noisy biological environments.

To strengthen the practical application, several lightweight and robust on-node processing strategies can be used to create reliable biosensing in resource-constrained environments. First, finite impulse response/infinite impulse response or adaptive filters can make noise suppression that decreases high-frequency interference and baseline drift in wearable settings (for example, mouthguards, contact lenses, masks and patch sensors)⁹⁶. Second, artefact rejection can isolate analyte-specific redox peaks and increase the signal-to-noise ratio in electrochemical biosensors. For example, differential pulse voltammetry can be used to distinctly reduce the background by sampling before and after each test⁹³. Third, the combination of anomaly detection and multimodal analysis (for example, pH, temperature and metabolites) can confirm physiologically implausible results. Fourth, multimodal data fusion and machine learning approaches with SHAP (SHapley Additive exPlanations) analysis can improve the interpretability of individualized model adaptation⁹⁷. Finally, prediction uncertainty can be estimated by using Bayesian-optimized models to generate confidence intervals, providing decision-makers with both accurate estimates and reliability measures⁹⁶. These advances demonstrate that in situ biosensing platforms not only ensure high-quality biochemical signal acquisition but also deliver interpretable, individualized and uncertainty-aware outputs, thereby enhancing their clinical and field decision-support utility.

The architecture and integration of in situ biosensors encapsulate a multifaceted approach combining advanced sampling, precise interference exclusion, dynamic enrichment, auto-calibration and cutting-edge signal enhancement to overcome the physical and biochemical barriers inherent in real-time monitoring (Supplementary Tables 3 and 4). These innovations establish a robust platform for accurate, continuous detection of analytes in complex matrices, laying the groundwork for future biosensors that are both highly sensitive and resilient. By shifting focus towards physical mechanisms in sampling and enrichment and biomimetic plus hardware solutions for signal fidelity, this integrated paradigm exemplifies a new era of biosensing technology poised to transform clinical diagnostics and environmental monitoring.

Extending the longevity of in situ biosensing

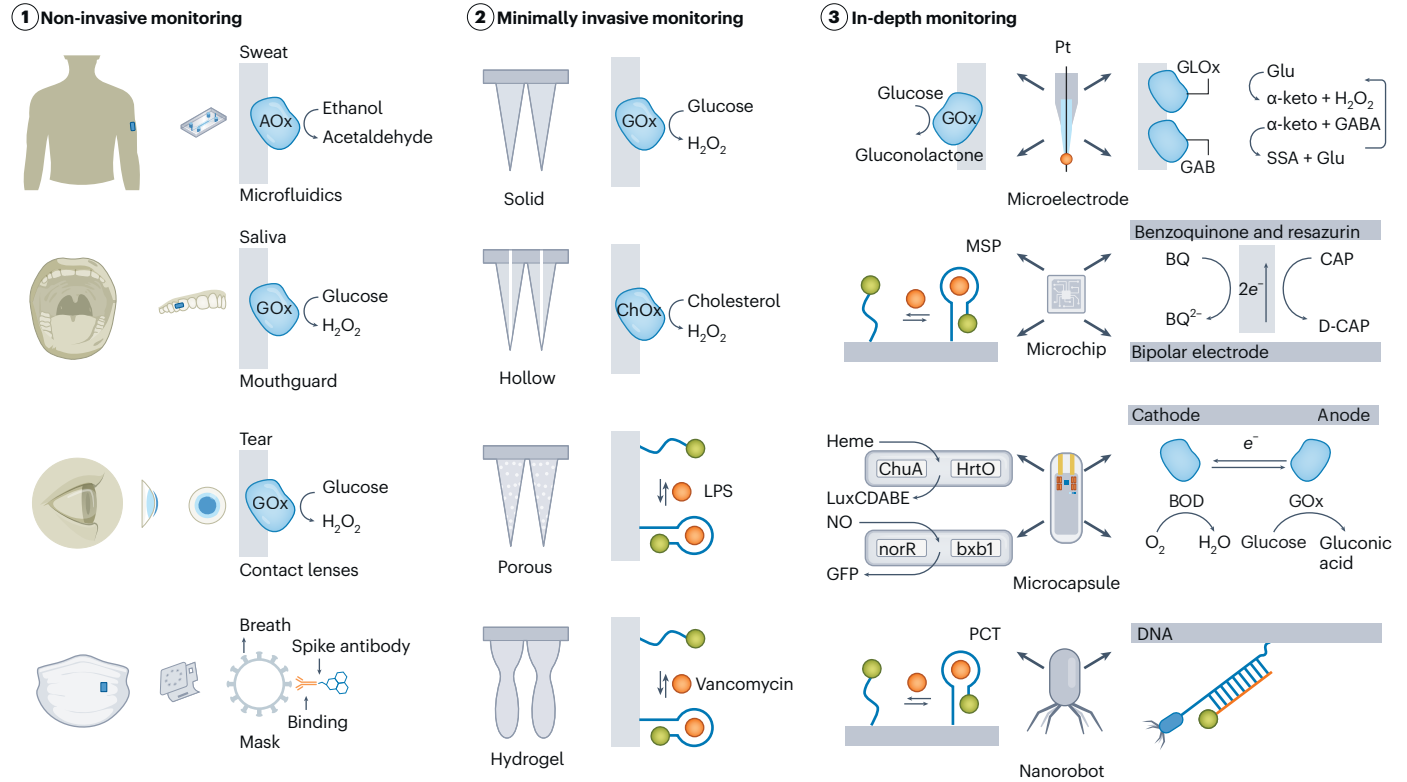
The functional longevity of in situ biosensors is predominantly limited by two interconnected factors: surface biofouling and the host's FBR, especially in complex biological or environmental settings. Biofouling leads to signal drift and sensitivity loss through the non-specific adsorption of biomolecules, while the FBR alters the local microenvironment and can isolate the sensor from its target analytes. The path to longevity requires strategies to mitigate biofouling and enhance biocompatibility to ensure the proper analytical performance of in situ biosensing.

Antifouling properties are critical for long-term in situ biosensing in complex environments, such as heterogeneous bodily fluids and natural environments. Biofouling and surface contamination occur when a fouling layer, formed by the non-specific adsorption of proteins, cells and other biomolecules (for example, from sweat or skin lipids), creates a barrier that physically blocks analyte access to recognition elements, causing substantial signal drift and a loss of sensitivity. For example, a key challenge for implanted electrochemical sensors is protein adsorption and cellular adhesion at the sensor–tissue interface, which directly leads to the loss of accuracy over time⁹⁸.

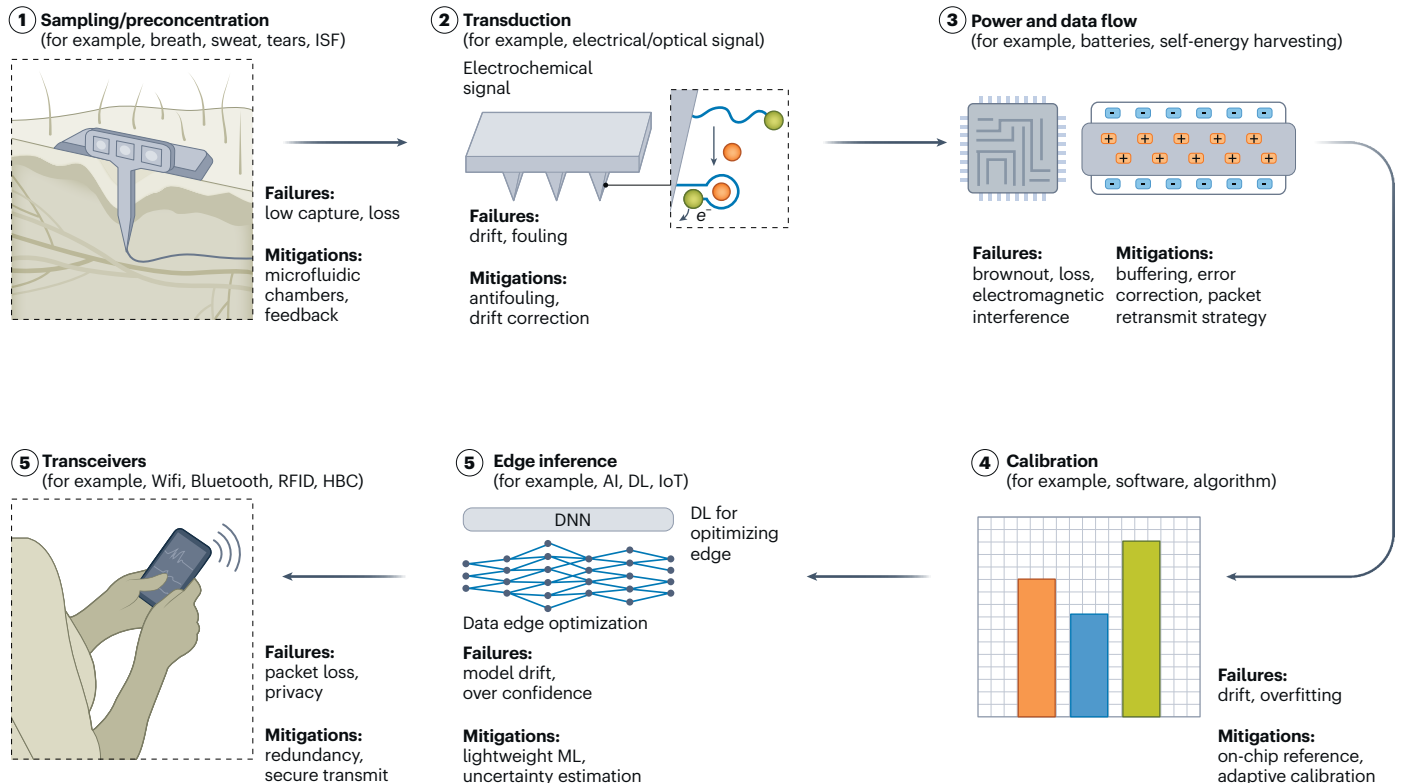
Currently, three strategies (chemical, biological and physical antifouling) can decrease the influence of biofouling and increase the lifetime of in situ biosensing (Supplementary Table 5). One of the most frequently utilized approaches to provide these biosensing interfaces with biofouling inhibition performance is using chemical strategies with highly polar, hydrated chemical polymers. Various chemical modifiers, for example, PEG and its derivatives (molecular weight <5 kDa)^{99,100}, zwitterionic polymers (poly(sulfobetaine methacrylate), poly(carboxybetaine acrylamide) and poly(phosphorylcholine))^{101,102}, antifouling peptides (for example, EKEKEKE, CPPPP-EKEKEKE, NQNQNQNQ, CRERERE and amphiphilic CYSYSYS)^{103,104}, and other self-assembled monolayer or hydrogel polymers (for example, hyaluronic acid, poly(hydroxy acrylates), poly(2-methyl-2-oxazoline), hyperbranched polyglycerol)¹⁰⁵, as well as composite materials (for example, phosphorylcholine/hyaluronic acid, PEG/sulfobetaine, peptide/hyaluronic acid)^{105,106}, can shield the binding of non-specific biomolecules from the interface of biosensing. For example, a zwitterionic coating applied to continuous glucose monitors through an integrative chemistry strategy substantially mitigates signal interference and enhances sensor performance¹⁰⁷. This zwitterionic polymer-coated sensor can accurately detect target glucose levels in murine models and non-human primates (both health and diabetic populations), without the need for recalibration following the initial blood glucose assessment that typically converts raw data to nominal values.

Beyond chemical strategies that rely on extensively hydrated interfacial materials, physical modifications of sensor interfaces have emerged as effective approaches to mitigate biofouling in complex environments. These physical strategies focus on manoeuvring molecular selective layers, such as the biocompatible polymer membrane and nanostructure of the sensor, to minimize the effect of biofouling. One approach, called the E-AB sensing platform, involves coating the sensor with membranes (for example, polysulfone and electro-grafted silica nanoporous)^{108,109} that allow for the rapid transport of analytes while simultaneously preventing biofouling agents from obstructing the sensor interface. Notably, using these membranes, the sensing platform with redox reporter-modified aptamer can achieve a long-term stable in vivo response in complex physiological and neurological environments. Another strategy, utilizing a similar effective antifouling method, is the nanoporous gold platform, which uses hydrophilic nanostructures that serve to block adsorption, denaturation and unfolding, while allowing the transport of target analytes and reporter probes¹¹⁰. In this approach, unlike the planar gold platforms, nanoporous gold electrodes (with pore size <50 nm) show a more antifouling ability in the presence of bovine serum albumin and fibrinogen. These antifouling

a Miniaturization strategies for in situ biosensing



b System pipeline of in situ biosensing workflows



strategies provide a potential way to mitigate fouling by limiting the accessibility of large biomolecules to the sensor interface.

In contrast to chemical and physical approaches, which predominantly depend on passive mechanisms to mitigate non-specific adsorption, the biological strategy directly reduces the concentration of

interfering agents, such as physisorbed (bio)molecules, via enzyme degradation on the sensor interface. By immobilizing enzymes that selectively degenerate non-specific species, this strategy not only prevents their accumulation but also actively removes them. For example, a trypsin-enabled platform effectively suppresses protein fouling in

Fig. 3 | Miniaturization strategies for next-generation in situ biosensing and system pipeline of in situ biosensing workflows. **a**, (1) Non-invasive monitoring. Wearable biosensing platforms, including patches, contact lenses, mouthguards and facemasks, incorporate multi-analyte detection capabilities for continuous monitoring of biomarkers. (2) Minimally invasive monitoring. In situ biosensing mechanisms utilize enzymatic and aptamer-based detection strategies, such as GOx for glucose sensing and aptamer-based sensors for lipopolysaccharide (LPS) and vancomycin. These biosensors are integrated into microneedle arrays, including solid, hollow, porous and hydrogel microneedles, offering a minimally invasive approach for biofluid sampling and analyte detection. (3) In-depth monitoring. Advanced implantable biosensors leverage miniaturized gold microelectrodes modified with GOx or a combination of GOx and gamma-aminobutyric acid (GABA) enzymes for neurotransmitter and metabolic monitoring. Microchip-based implantable sensors facilitate real-time in vivo detection of biomarkers such as methylated septin 9 (MSP) and captopril (CAP).

In addition, nitric oxide (NO), haem and glucose sensors have been incorporated into microcapsule systems, while nanorobots engineered for in situ diagnostics are capable of navigating blood vessels for targeted detection of procalcitonin and DNA, representing a frontier in autonomous biosensing technology. AOX, alcohol oxidase; ChOx, cholesterol oxidase; GLOx, glutamate oxidase; GAB, GABA transaminase; SSA, succinic semialdehyde; BQ, benzoquinone; ChuA, cholesterol-uptake / Chu (haem uptake) A outer membrane transporter; HrtO, haem regulated transporter O; luxCDABE, luciferase gene cluster operon; GFP, green fluorescent protein; norR, a transcription factor specifically senses nitric oxide; bxb1, a recombinase; BOD, bilirubin oxidase; PCT, procalcitonin. **b**, System pipeline of in situ biosensing workflows (for example, sampling/preconcentration, transduction, power/data flow, calibration, edge inference, and transceivers) along with its concerns and solutions. RFID, radio frequency identification; HBC, human body communication; DL, deep learning, ML, machine learning.

dynamic flow processes, achieving over 15 days of resistance to protein fouling and demonstrating a flux recovery ratio of 100% after filtering protein solutions. This advancement brings in situ biosensing closer to practical application¹¹¹.

Integrating multiple antifouling strategies can considerably reinforce the performance and longevity of in situ biosensors in complex conditions. For example, preventing biomolecule adsorption on a brain-implanted biosensor surfaces poses a prominent challenge for in vivo neurochemical surveillance. An ultrathin film that mimics cell membranes (physical strategy), integrated with zwitterionic phosphorylcholine (chemical strategy) through electropolymerization on carbon fibre substrates, not only blocks non-specific protein adsorption but also maintains sensitivity and temporal dynamics for in vivo dopamine evaluation¹¹². The commercialization of electrochemical biosensing chips, however, has often been hindered by the rapid failure induced by the inactivation and biofouling of specific electrochemical biosensors. Another example is an affinity-based electrochemical technique that enables multiplexed measurements in complex biological environments for precision healthcare¹¹³. This platform uses a three-dimensional porous nanogold substrate (physical strategy) combined with cross-linked bovine serum albumin (chemical strategy) to generate a primitive antifouling coating, allowing efficient quantification of anti-IL-6 in plasma with only 10% signal loss after 1 month of storage in blood plasma or serum. This technique can also be extended to other affinity recognition systems, such as antigen-antibody interactions, facilitating the development of in situ biosensors for in-hospital diagnosis, environmental safety and implantable biosensing devices.

In addition to pervasive fouling, a key challenge for implantable biosensors is the FBR. Strategies to mitigate the FBR, such as 'passive coatings' and 'active release systems', are critical for

ensuring long-term biocompatibility ('Enhancing biocompatibility' in Supplementary Information).

Enhancing the capacity of in situ biosensing to be adopted

The widespread adoption of in situ biosensing technologies beyond research laboratories hinges on their seamless integration into diverse, real-world settings. This requires devices that are not only physically unobtrusive and user-acceptable but also capable of sustained, autonomous operation. Two fundamental pillars underpin this transition: the development of miniaturized platforms that enable comfortable, discrete and site-specific monitoring across the human body and environment; and the advancement of robust power sources that free these devices from tethers and frequent battery replacements.

Miniaturized platforms

The miniaturization of biosensing platforms is essential for effective in situ detection, enabling their deployment across various environments, including homes, clinics and on-site locations. The platforms can be categorized into three strategies based on their monitoring approach: (1) non-invasive monitoring on the body surface, (2) minimally invasive monitoring beneath the skin, and (3) in-depth monitoring within internal organs (Fig. 3 and Supplementary Table 3). The non-invasive monitoring has no limit for the size of the platform, ranging from millimetres to tens of centimetres. Unlike the non-invasive monitoring platform, the devices for minimally invasive (micrometre to millimetre) and in-depth monitoring (micrometre to centimetre) that are small and lightweight typically do not require complex surgeries or invasive procedures, reducing patient trauma and discomfort and enhancing the acceptability of the tests. To address safety and effectiveness

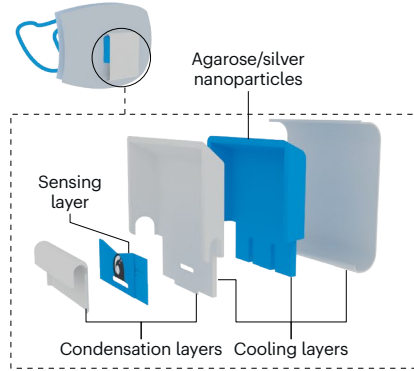
Fig. 4 | Architectures and integration strategies for in situ biosensors.

a, Masks. Smart EBCare mask⁸⁵: analyses exhaled breath biomarkers via tandem radiative cooling for efficient condensation. The wearable, freeze-dried, cell-free (wFDCF) mask⁵⁶: the system transports viral particles via winding material and the results are visualized on lateral flow assay (LFA) strips. Wireless pathogenic infection diagnosis system (PIDS)⁸⁶: battery-free, evolvable system diagnoses viral infections using an immune biosensor (IBS) module with graphene-enhanced signal transduction. μ PAD, microfluidic paper-based analytical device; NFC, near-field communication. **b**, Wearables. A flexible printed circuit board (FPCB) nanobiosensor³⁶: quantifies hormones in sweat via strand-displacement aptamer switches. Microneedle-based biosensor¹⁴: enables wireless, continuous ISF metabolite sensing via reusable electronics and a microneedle array. Scale bar, 75 μ m. Active-reset sensor³⁸: achieves continuous ISF protein monitoring within 1-minute intervals. RE, reference electrode; WE, working electrode; CE, counter electrode. **c**, Implantables. Aptamer-field-effect transistor (FET) neuroprobe¹⁴⁹: monitors serotonin in vivo using nanoscale FETs for enhanced sensitivity. SENSBIT system⁹⁴: enables long-term pharmacokinetic monitoring in blood via a biomimetic nano-bio interface. Aptamers on carbon

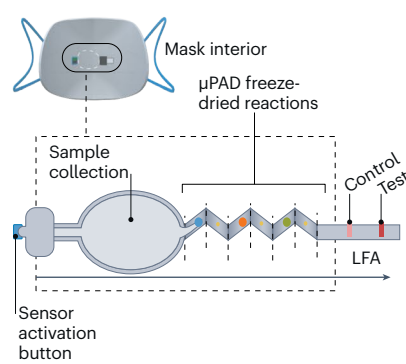
fibre microelectrodes (CFEs) (aptCFE_{2,0}) biosensor¹⁴⁷: facilitates stable in vivo dopamine neurosensing using electrochemically conjugated aptamers on carbon fibre electrodes. **d**, Capsules. IMBED⁷²: ingestible device detects haem using biosensor bacteria and wireless readout. Ingestible biofuel cell (BFC) sensor⁷⁴: self-powered capsule monitors intestinal glucose metabolites via biofuel cell energy harvesting and magnetic human body communication telemetry. Sub-1.4-cm³ sensor⁷³: tracks inflammation molecules using engineered probiotics integrated with a photodetector/readout chip. PU, polyurethane; mHBC, magnetic human body communication. Panels adapted with permission from: **a**, ref. 85 (smart EBCare mask), AAAS; ref. 56 (wFDCF mask), Springer Nature Limited; ref. 86 (wireless PIDS) under a Creative Commons licence CC BY 4.0; **b**, ref. 36 (FPCB nanobiosensor), Springer Nature Limited; ref. 14 (microneedle-based biosensor), Springer Nature Limited; ref. 38 (active-reset sensor), AAAS; **c**, ref. 149 (aptamer-FET neuroprobe) under a Creative Commons licence CC BY 4.0; ref. 94 (SENSBIT system), Springer Nature Limited; ref. 147 (aptCFE_{2,0} biosensor), Wiley; **d**, ref. 72 (IMBED), AAAS; ref. 74 (ingestible BFC sensor) under a Creative Commons licence CC BY 4.0; ref. 73 (sub-1.4-cm³ sensor), Springer Nature Limited.

a Masks

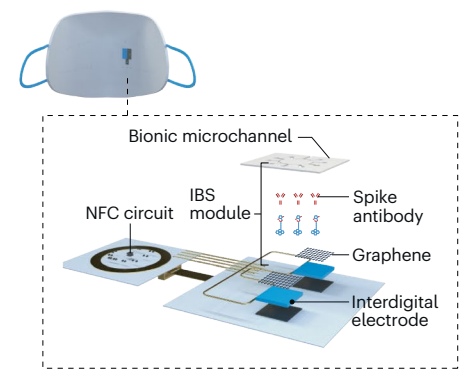
Smart EBCare mask



wFDCF mask

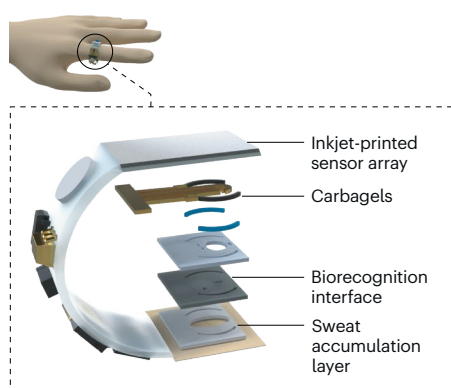


Wireless PIDS

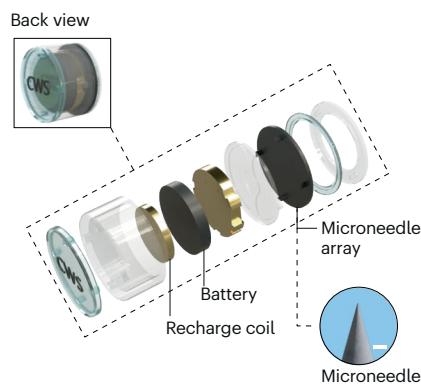


b Wearables

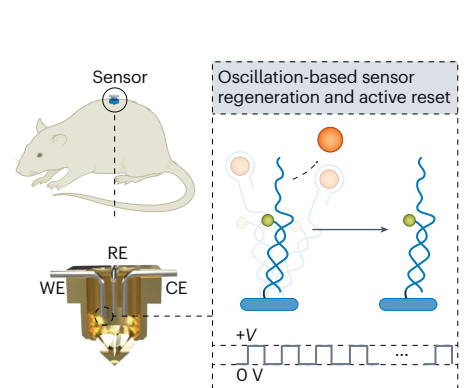
FPCB nanobiosensor



Microneedle-based biosensor

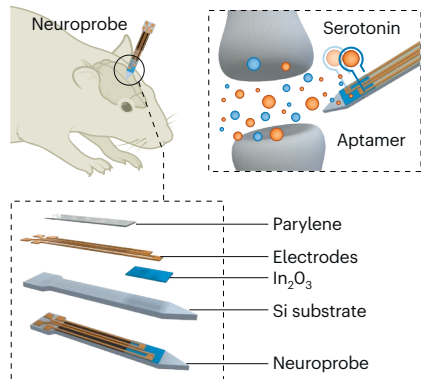


Active-reset sensor

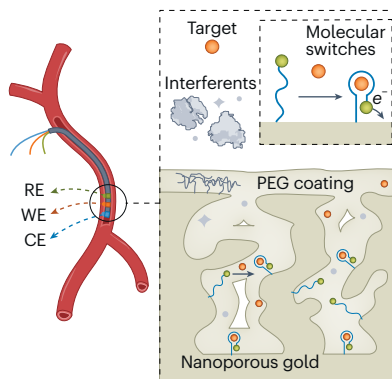


c Implantables

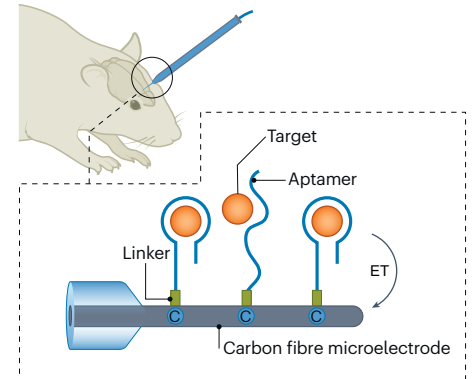
Aptamer-FET neuroprobe



SENSBIT system

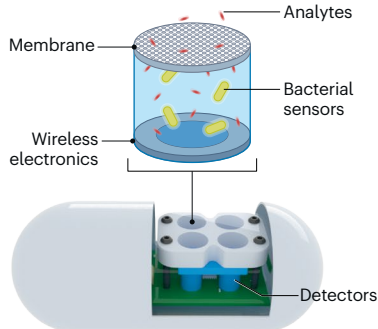


aptCFE_{2.0} biosensor

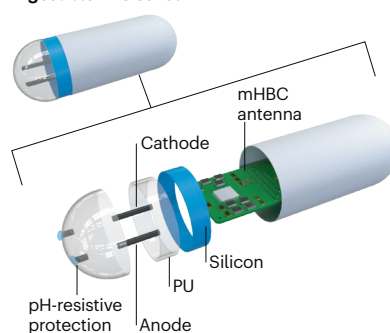


d Capsules

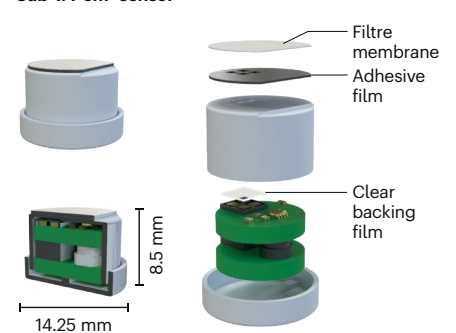
IMBED



Ingestible BFC sensor



Sub-1.4-cm³ sensor



concerns, the US Food and Drug Administration has implemented a specific programme of controls to ensure the safety and efficacy of these platforms for in vivo testing on humans and animals.

Non-invasive monitoring (Figs. 3a and 4a), such as facemasks, medical mouthguards, smart contact lenses and IoT-sensing coatings on the body surface, primarily focuses on diagnosing substances such as tear fluids, sweat and respiratory gases¹¹⁴. This shift to wearable technology supports integration into daily life, enhances health management, enables continuous monitoring of long-term drug pharmacokinetics and empowers users to track their well-being without the need for surgical procedures. The skin, as the largest organ of the body, serves as an ideal interface for extracting biomarkers, as it regulates thermal and environmental responses through perspiration, which contains a variety of ions, metabolites, proteins and hormones¹¹⁴. This makes the skin an essential platform for extracting physical and chemical biomarker information relevant to health monitoring. Beyond skin-based applications, wearable biosensors are making important strides in oral health monitoring, utilizing saliva as a medium for non-invasive detection of various biomolecules, including metabolites, proteins, hormones and microorganisms, which are scientifically correlated with blood levels of specific biomarkers, including glucose and cortisol¹¹⁵. These biosensors, such as mouthguard enzymatic biosensors¹¹⁶ and a peptide–graphene nanosensor integrated into tooth enamel¹¹⁷, provide valuable insights into hydration status, metabolic health and disease detection, offering an alternative to traditional blood tests. Challenges, however, remain in saliva sensing owing to analyte dilution, complications from mucus and contamination from everyday oral activities^{7,115}. Ocular biosensing represents another promising area in wearable technology, primarily using contact lenses and patches for health monitoring¹¹⁸. Similar to saliva, tear fluid contains a broad range of substances, making tear-based biosensors valuable for analysing ocular health and systemic conditions¹¹⁹. In parallel, breath analysis is emerging as a powerful tool for detecting respiratory biomarkers, as exhaled breath contains over 3,500 substances (for example, volatile organic compounds, nucleic acids, metabolites and proteins) and presents a reliable correlation between blood and breath levels of various analytes, with devices (for example, smart facemasks) capable of analysing exhaled breath providing real-time insights into metabolic processes (for example, chronic obstructive pulmonary disease) and potential pathogens (for example, SARS-CoV-2, influenza A H1N1 and respiratory syncytial virus)^{56,120}. Unfortunately, the challenge related to sample collection in the facemask hinders the widespread application of in situ analysis. Compared with a traditional sample collection strategy that depends mainly on bulk ice buckets or refrigeration, the new tandem cooling system unites hydrogel evaporative cooling (agarose hydrogel) and metamaterial radiative cooling (ceramic alumina–polymer hybrid metamaterial) for EBC. The EBC analysis and respiratory evaluation (EBCare; Fig. 4a and Supplementary Fig. 2) can automatically capture, transport and continuously monitor multiple biomarkers (for example, NH_4^+ , pH, alcohol and NO_2^-) across real-life activities⁸⁵. Some other substantial challenges remain for breath analysis, including low analyte concentrations and the complex chemical composition of breath that complicates detection; in addition, further data collection and analysis are necessary to establish comprehensive correlations between breath and blood biomarkers, while real-time sensing continues to pose major challenges¹²¹.

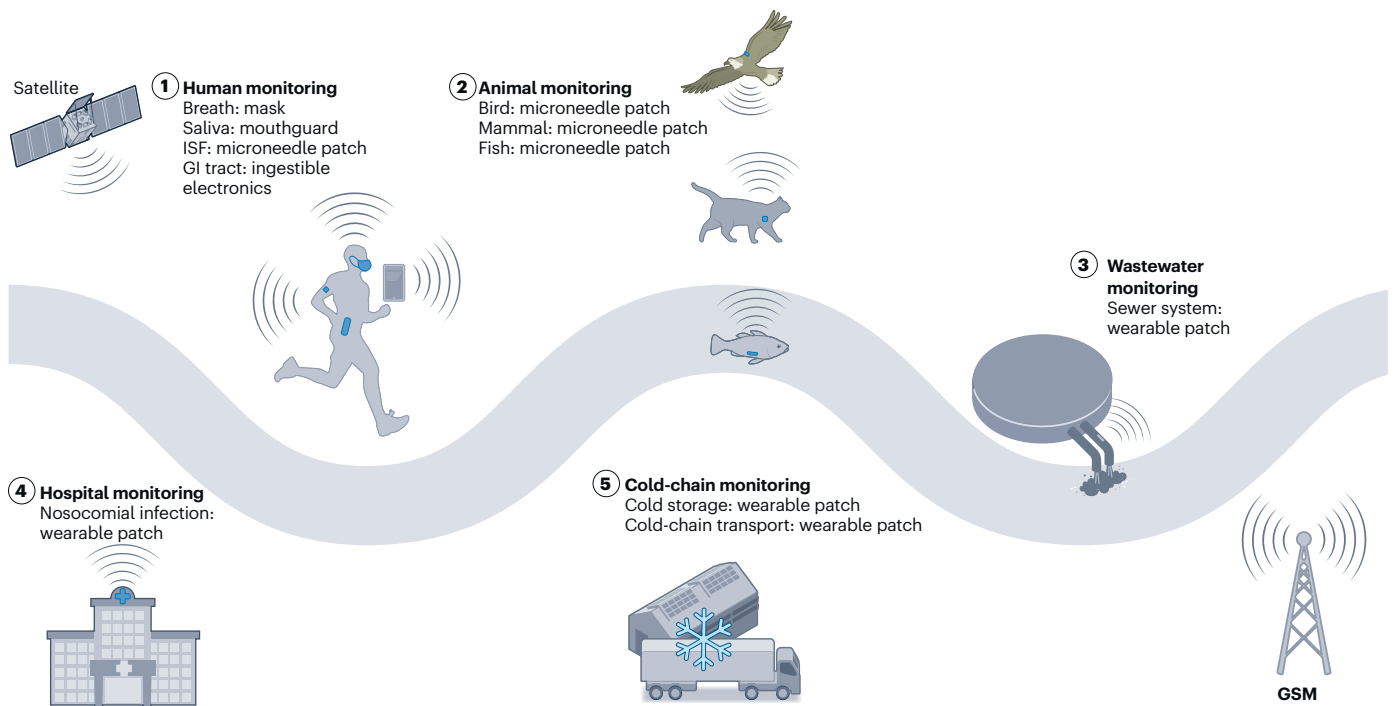
In contrast, minimally invasive biosensors utilize ISF by placing sensors just beneath the surface of the skin, allowing for continuous tracking of critical biochemical markers (Figs. 3a and 4b), including glucose levels¹²² and drug pharmacokinetics¹²³. While sweat is valuable for health monitoring, direct analysis of ISF provides greater accuracy and reliability owing to its strong correlation with blood concentrations for relevant biomarkers¹²⁴. In this case, minimally invasive monitoring, such as microneedles beneath the skin, is the most appropriate. Owing to their minuscule size (0.1–1.3 mm), microneedles, such as solid, hydrogel, hollow and porous types, can penetrate the skin without contacting pain-sensing nerves, thereby mitigating pain and discomfort¹²⁵. These minimally invasive devices contribute substantially to personalized health management and timely medical interventions. For example, a solid stainless steel microneedle system (820 μm) can extract ISF at a rate of 2.9 μl within 30 seconds¹²⁶; however, its susceptibility to corrosion in biological environments raises concerns regarding long-term stability. In contrast, hydrogel microneedles (1,266 \pm 91 μm) effectively extract ISF (1.25 \pm 0.37 mg in 10 minutes) without corroding and penetrating the dermis layer¹²⁷. Monitoring the levels of individual biomarkers (for example, glucose) within the blood and ISF has become inadequate to address the complex demands of modern healthcare. Consequently, the integration of microneedles (850 μm) with graphene oxide-nanoparticle-based fluorescent biosensors now permits the concurrent diagnosis of various analytes (for example, glucose and uric acid) in vivo, offering a more comprehensive approach to medical diagnostics and personal health monitoring¹²⁸. These advancements underscore the potential of minimally invasive biosensors to bridge the gap between non-invasive and fully implantable systems, offering high-precision, real-time target tracking with a minimal patient burden.

While non-invasive and minimally invasive biosensors effectively track biomarkers at the body surface and within ISF, precise and continuous biomarker monitoring within deep tissues and organs remains a major challenge. To address this, miniaturized in-depth biosensing platforms, categorized as stationary (for example, microelectrodes and microchips) and movable (for example, microcapsules and nanorobots; Figs. 3a and 4c,d), have been developed for applications in the brain, abdominal organs and GI tract. Stationary platforms are designed to be implanted in a specific location within the body, such as the sub-epidermis or vital organs such as the brain and the heart. These sensors continuously monitor critical biomarkers (for example, physiological parameters, metabolites and neurochemicals)^{129,130}, providing healthcare professionals with real-time data that aid in managing conditions such as diabetes and cardiovascular diseases, ultimately supporting timely interventions. The biosensors implanted under the skin, especially in the bloodstream, could study the patient's health and their response to therapeutics, wherein the drugs could be tailored with optimal doses for patients to maximize efficacy and minimize side effects (for example, doxorubicin, kanamycin and methotrexate)^{131,132}. In addition, stationary platforms have been developed for real-time pharmacokinetic monitoring of drugs (for example, vancomycin¹³³ and irinotecan¹³⁴) and metabolites (for example, phenylalanine²⁹), contributing to precision-medicine approaches. While these platforms enable continuous monitoring for up to hours or several days, further experimental data are needed before being utilized in clinical settings. In addition to a stationary platform implanted under the skin, specialized organ biosensors have been developed to monitor vital parameters

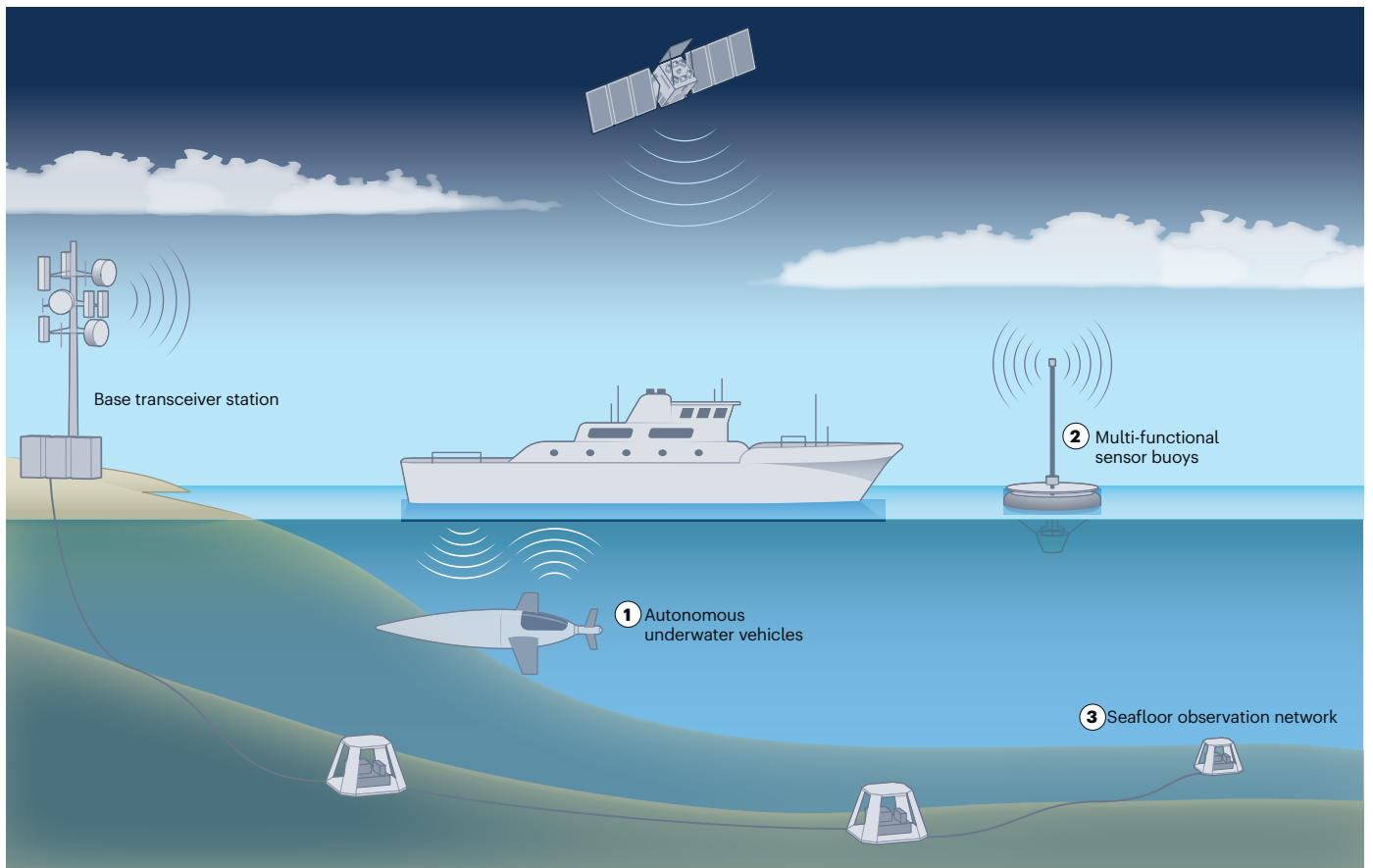
Fig. 5 | IoT and AI-enabled in situ biosensing for pathogenic infection and marine microbiology monitoring. **a**, IoT and AI-enabled biosensing platforms provide continuous, real-time detection across diverse biological matrices and settings, including human specimens, animals, wastewater, healthcare settings and cold-chain environments. By continuously monitoring health indicators, the system provides real-time alerts for emerging infectious threats, thereby enabling timely and targeted public health interventions. GSM, global system

for communication. **b**, Marine applications leverage networked autonomous and stationary platforms to characterize microbial communities and their environmental drivers: mobile autonomous underwater vehicles conduct in situ microbial sampling, multi-functional sensor buoys provide continuous surface and near-surface monitoring of microbial dynamics and water quality, and seafloor observation networks of stationary sensor arrays enable long-term microbiological surveillance on the seabed.

a IoT and AI-driven in situ biosensing for pathogenic infection



b IoT and AI-driven in situ marine monitoring for microbiology



in specific organs, such as the brain and the heart. These devices track neurochemicals (for example, dopamine, serotonin, glutamate and lactate)¹³⁵ that are crucial for neuronal communication and profoundly influence brain function and activity, thereby aiding in understanding disease progression and treatment efficacy. In parallel, movable biosensing platforms, such as ingestible biosensors and nanorobots, offer strategies for GI and vascular monitoring. Ingestible biosensors enable real-time assessment of GI functions (Fig. 4d and Supplementary Fig. 2), including temperature monitoring¹³⁶, endoscopy¹³⁷ and pH levels¹³⁸, serving as an alternative to invasive endoscopic procedures. Meanwhile, nanorobots also offer an in-depth monitoring method for blood vessel biosensing, particularly in small portions deep inside the body of the host, owing to their high fluidity and controllability, allowing for in situ detection of circulating biomarkers and disease diagnostics. While both stationary and movable biosensing platforms offer the transformative potential for in-depth biomarker monitoring, further advances in miniaturization, biocompatibility and long-term stability will be crucial for clinical translation and widespread adoption in precision healthcare.

Advancing in situ biosensing requires solutions that extend beyond miniaturization, crucially depending on sustainable power sources and IoT and AI integration. While power solutions, from batteries to energy harvesting, address the critical bottleneck of energy consumption for device longevity and autonomy, IoT and AI collectively enhance sensor intelligence by enabling real-time data transmission, smart analysis and predictive decision-making ('Power source' and 'IoT & AI-driven in situ biosensing' in Supplementary Information).

Outlook

The rapid innovation of in situ biosensing technologies is revolutionizing medical healthcare, food safety and environmental monitoring by enabling real-time, continuous and decentralized biomarker monitoring. These advancements are driving a transition from conventional laboratory-based ex situ detection to dynamic, on-site biosensing systems that speed immediate decision-making and early warning interventions. Historically, the shift from ex situ to in situ biosensing has been slowed down by technological, regulatory and biocompatibility challenges. Key technological enablers of this acceleration include microelectronics and miniaturization, biodegradable and smart biomaterials, and wireless connectivity and AI integration.

A critical frontier lies in enhancing the biocompatibility and long-term stability of implantable biosensors. Key challenges include mitigating the FBR and eliminating the need for complex surgical removal. The improvement of biodegradable implants, using materials such as natural and synthetic polymers (for example, decellularized extracellular matrix, silk and polylactide)¹³⁹ and hydrolysable metals (for example, Zn-based or Mg-based biodegradable materials)¹⁴⁰, represents a promising direction. However, major hurdles remain, including precise control over degradation rates, maintenance of mechanical integrity and consistent sensor performance during dissolution.

Looking forward, the future of in situ biosensing lies in the integration of multimodal hybrid platforms that combine optical, mechanical, biochemical and electrical sensing modalities into packed wearable or implantable systems¹⁴¹. Miniaturization raises several functional and engineering challenges: high energy demands can negotiate battery longevity, requiring efficient power management tools that adjust sensor functionality with user mobility; electromagnetic crosstalk and interference among densely compact biosensors can impair data accuracy, calling for progressive noise reduction and precise voltage and current modulation methods (for example, the requirement of system-on-chips and microcontroller units for wireless transmission)¹⁴²; and the complex integration of heterogeneous data modalities, requiring precise synchronization, rigorous preprocessing and robust validation metrics to assure consistency and accuracy amid calibration errors and environmental variability. User-specific factors (for example,

variations in body type, skin thickness, adherence, comfort and device aesthetics)^{141,143} further challenge the long-term application of these in situ biosensors into daily life.

For in situ biosensing technologies to accomplish across-the-board, addressing regulatory, ethical and privacy concerns is critical. Regulatory frameworks must adapt to the rapid pace of development, ensuring that biosensing systems meet reliability, safety and clinical validation criteria. The collection and analysis of sensitive health data raise fundamental issues, including informed consent and data ownership, requiring robust legal and ethical structure to ensure individual rights. As in situ biosensing platforms increasingly integrate with AI and IoT technologies¹⁴⁴, concerns over online security and data breaches further underscore the requirements for advanced encryption and secure data transmission strategies. Addressing these multifaceted issues is essential for the widespread adoption of in situ biosensing solutions, ultimately promoting their integration into public health initiatives and clinical practice.

In situ biosensing technologies are poised to revolutionize healthcare and environmental monitoring. A compelling vision for the future lies in the integration of IoT and AI-driven platforms across multiple domains, forming a continuous and intelligent monitoring network (Fig. 5a). Such systems could seamlessly connect human-focused detection—using smart masks for breath analysis, mouthguards for salivary biomarkers, microneedle patches for ISF and ingestible electronics for GI tract monitoring—with animal-borne wearables and distributed environmental monitors in wastewater, clinical and supply-chain settings. These interconnected nodes, linked by satellite, cellular and Wi-Fi communications, enable continuous data flow across biological and geographical scales. Existing implementations include the Environmental Sample Processor (MBARI)¹⁴⁵, which performs automated, subsurface analyses, to identify marine microbes and toxins in real time. Meanwhile, marine biosensing systems increasingly use base transceiver stations, multifunctional sensor buoys, autonomous underwater vehicles and seafloor observation networks for robust real-time monitoring (Fig. 5b). These advances highlight a shift towards fully connected, adaptive biosensing infrastructures capable of delivering precise, timely insights from individual health to ecosystem scale.

The next decade will witness transformation in in situ biosensing. These advancements will redefine health management and environmental monitoring, ultimately enabling a distinct shift towards predictive and personalized medicine. By overcoming current technical, regulatory and ethical challenges, next-generation in situ biosensing technologies will serve as fundamental tools for ensuring global health security. The future of biosensing is no longer confined to the laboratory; it is becoming an integral part of everyday life, clinical practice and public health infrastructures.

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Y.W., B.W., F.G. and R.L.-A. conceptualized the project. B.W., Y.W., A.S., Z.L., J.F., A.M., X.Z., M.Y., L.Q., A.L., Z.Y., F.S., J.H., S.Z. and C.M. researched data for the article. B.W., Y.W., Z.L., X.Z., M.Y., L.Q. and A.S. contributed to the original writing. Y.W., B.W., A.S., F.G. and R.L.-A. were involved in writing, reviewing and editing.

All authors made a substantial contribution to the discussion and approved the final version for submission.

Competing interests

The authors declare no competing interests.

Additional information

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