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50 Years of Biosensing Development and Prospects: Postprint

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Abstract

Biosensors are analytical devices composed of biological elements and physical/chemical transducing components, representing typical interdisciplinary and convergent technologies. Biosensors exhibit characteristics of rapidity, accuracy, and simplicity, and have achieved high-throughput analysis through microarray platform technology (biochips), holding broad application prospects in life science research, disease diagnosis and monitoring, bioprocess control, agriculture and food safety, environmental quality monitoring, biosafety and biosecurity, among other fields. After 50 years of development, biosensing has entered a new stage of vigorous growth, with the primary driving factors being the proposal and implementation of concepts such as Big Health, Internet of Things, and Big Data; research hotspots include wearable and portable devices, point-of-care testing (POCT), non-invasive analysis, in vivo measurement, online detection, on-site monitoring, ultra-high spatiotemporal resolution, and single-cell biology applications, among others. Different application scenarios present distinct technical challenges, among which the stability of biological elements is a common issue that remains to be addressed. Chinese scholars' research publications in the field of biosensing have generally entered the international first tier in terms of impact; the next objective is to achieve academic excellence and leadership, while substantially enhancing global market development capabilities to contribute to Big Health.

Full Text

Special Issue Preface: Biosensors & Organs-on-Chips

Biosensing and organs-on-chips both belong to the category of biological devices, representing typical interdisciplinary products and convergence technologies. Biosensing has developed over the years, playing important roles in life science research, disease diagnosis and care, environmental monitoring, and biological process control. Organs-on-chips, an emerging technology developed in

recent years, represent a new direction for biochips and hold significant application prospects in new drug development, toxicology research, and regenerative medicine. Currently, as the One-Health concept moves from theory to implementation, it has endowed biosensing and organs-on-chips with new momentum. The integrated development of both technologies holds great significance for the advancement of life sciences and the One-Health cause. The *Bulletin of Chinese Academy of Sciences* has specially organized this “Biosensors & Organs-on-Chips” special issue, aiming to further attract attention from relevant national management departments and the public to this field. This special issue was guided and advanced by editorial board member Professor Zhang Xian-En from the Institute of Biophysics, Chinese Academy of Sciences.

Abstract

Biosensors are analytical devices composed of biological elements and physical/chemical transducers, representing typical interdisciplinary and convergence technologies. Biosensors feature rapid, accurate, and simple characteristics, and have achieved high-throughput analysis through microarray platform technology (biochips). They hold broad application prospects in life science research, disease diagnosis and monitoring, biological process control, agriculture and food safety, environmental quality monitoring, biosafety and biosecurity, and other fields. After 50 years of development, biosensing has entered a new phase of vigorous growth, driven primarily by the introduction and implementation of concepts such as One-Health, Internet of Things, and big data. Research hotspots include wearable and portable devices, point-of-care testing (POCT), non-invasive analysis, in vivo detection, online monitoring, field monitoring, ultra-high spatiotemporal resolution, and single-cell biology applications. Different application scenarios present different technical challenges, among which the stability of biological elements is a common issue yet to be overcome. Chinese scholars' research papers in the biosensing field have overall entered the international first tier. The next goals are to achieve academic excellence and leadership, and to significantly enhance global market development capabilities, contributing to One-Health.

Keywords: biosensing, One-Health, wearable, non-invasive analysis, in vivo detection, molecular biosensing, nanobiosensing, high spatiotemporal resolution

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50 Years of Biosensor Development and Prospects

1960s: The Birth of Biosensors

In the 1960s, American electroanalytical chemist Leland C. Clark Jr. posed the question: could the determination of biochemical substances be as convenient as using a pH electrode? This led to the emergence of the enzyme electrode—the first biosensor [1-3]. Over the past half-century, principles and technologies from multiple disciplines including life sciences, chemistry, physics, information science, materials science, and bionics have converged, transforming biosensing into a typical convergence technology. Characterized by simplicity, sensitivity, speed, and accuracy, biosensing has demonstrated broad application prospects in life science research, disease diagnosis and home care, biological process control, agriculture and food safety, environmental monitoring and pollution control, biosafety and biosecurity, as well as aerospace, deep-sea, and polar sciences (Table 1).

Development Stages and Characteristics

First Development Peak: Adoption of Various Physical and Chemical Transduction Principles Drives Field Formation During the 1970s-80s, on one hand, various biological macromolecules and biomaterials were selected as molecular recognition elements for biosensors, including enzymes, antibodies, nucleic acids, cells, tissue slices, microorganisms, and intact biological organs (such as animal neural antennae), enabling rapid detection of numerous biochemical and immunological substances (i.e., environmental chemicals). On the other hand, numerous physical and chemical transducer principles were adopted, forming a large biosensing family. This encompassed conversions from biological mass to various physical and chemical quantities, including electrochemical biosensing, thermal biosensing, semiconductor biosensing (bio-field-effect transistors), optical fiber biosensing, piezoelectric, mass, and acoustic wave biosensing. These novel biosensing modes, each with distinctive features suitable for different application scenarios, established the developmental framework for the biosensing field (Figure 1 [Figure 1: see original paper]).

Second Development Peak: Novel Biosensing Principles and Large-Scale Commercialization During the 1980s, three major developments characterized this period:

(1) Commercial success of second-generation enzyme electrodes. In the 1980s, the American company YSI (Yellow Spring Instruments Inc.) achieved commercial application of enzyme electrodes in the food fermentation industry. However, early enzyme electrodes faced two major challenges for wider adoption: First, the enzymes employed were mostly oxidoreductases, particularly oxygen-dependent enzymes that use oxygen molecules as electron acceptors, requiring high operating potentials (0.7 V). This made them susceptible to interference from other electroactive substances, and variations in

background oxygen concentration in samples also generated noise. To address this, British scholar Cass et al. [4] replaced oxygen molecules with the synthetic chemical mediator ferrocene as the electron acceptor for enzyme catalysis, enabling electron transfer between enzyme and electrode at lower potentials. This solved the problems of electroactive interference and oxygen background noise, giving rise to the so-called second-generation enzyme electrode. Second, enzyme electrodes were handmade, resulting in high costs and poor interchangeability, limiting their widespread promotion. Inspired by printed circuit technology in the electronics industry, experts at Cranfield University in the UK introduced screen-printing technology to enable large-scale preparation of enzyme electrodes. The combination of new principles and new technologies successfully resolved these challenges, transforming biosensors into disposable, single-use commodities. This technology was first applied to blood glucose measurement, rapidly gaining popularity in hospitals and widely used for home care by hyperglycemic patients.

(2) Surface plasmon resonance (SPR) biosensors [5] for biomolecular interaction studies. Life science research and drug development extensively require the measurement of biomolecular interactions. In SPR sensors, when incident light undergoes total internal reflection, its optical energy resonates with the surface electron cloud of the device. The resonance angle shifts in correlation with interactions between biomolecules on the device surface and target molecules. The measurement process enables real-time dynamic monitoring without sample labeling, with sensitivity comparable to radioimmunoassay. The Swedish Biacore biosensing instrument (now part of GE) based on this principle has become an effective tool and dominant technology for studying biomolecular interactions. However, every technology has its lifecycle. In the past decade, ForteBio has introduced another label-free technology—bio-layer interferometry (BLI) [6]. This method features low cost and high throughput, rapidly gaining widespread application and competing with SPR biosensing.

(3) DNA chips enabling high-throughput gene expression analysis. Biochips include computer biochips, lab-on-a-chip, and detection chips. Among them, detection chips can be considered the high-throughput form of biosensing. DNA chips that emerged in the mid-1990s feature microarray densities of up to tens of thousands of DNA probes per square centimeter, enabling one-time acquisition of whole-genome expression profiles and becoming an important tool in life science research [7]. Affymetrix is the flagship company in this field. Based on DNA microarray chips, a series of biochips have been developed, including protein chips, peptide chips, oligosaccharide chips, and immunoassay chips, widely used in research and clinical applications. Domestic research centers and enterprises such as CapitalBio, originating from Tsinghua University, have also made innovative contributions and successfully developed markets. According to market analysis reports, the global markets for biosensing and biochips were \$12.9 billion and \$3.9 billion respectively in 2014, and are projected to reach \$22.5 billion and \$18.4 billion by 2020, with compound annual growth rates of 9.7% and 31.6% [8,9], representing a total market size of approximately \$40

billion.

Third Development Peak: Nanotechnology Widely Applied to Enhance Biosensing Sensitivity and Multifunctionality Since the 21st century, the introduction of nanotechnology has endowed biosensing with many new characteristics, such as high sensitivity, multi-parameter detection, and microenvironment applications [10]. Nanoscale effects include surface effects, small-size effects, and macroscopic quantum tunneling effects. When sensors or sensor components reach the nanoscale, these effects manifest to varying degrees: at nanoscale dimensions, the percentage of surface atoms at the sensing interface increases significantly, enhancing sensor sensitivity. Small-size effects lead to changes in optical, thermal, magnetic, and mechanical properties. For example, semiconductor nanocantilevers can weigh a single virus particle (9.5×10^{-15} g) [11]. Similarly, semiconductor quantum dots exhibit emission frequency changes with size under the same excitation wavelength, enabling simple multi-target optical detection by adjusting quantum dot size. Due to their much stronger photobleaching resistance compared to fluorescent dyes and proteins [12], quantum dots are suitable for long-term observation and have gained widespread application in life science research and disease diagnostics.

Proteins and DNA are natural nanomaterials. Through self-assembly, they form exquisitely structured and uniquely functional biosensing networks and molecular machine systems within cells, ensuring orderly metabolism. Understanding their complex structures and operational mechanisms is crucial for deepening our comprehension of life phenomena. Moreover, based on this knowledge, constructing nanobiosensors or hybrid nanobiosensors combined with nanomaterials is particularly suitable for studying biological processes in living cells and the development of major diseases. Nanobiosensing has generated numerous research reports and become an important research direction in nanobiology and nanobiotechnology.

According to Web of Science database (Clarivate Analytics) statistics, among over 60,000 biosensing-related papers published since 2010, 58% concern nanobiosensing or biosensing employing nanotechnology. Novel nanomaterials such as graphene, carbon nanotubes, and quantum dots significantly enhance biosensor performance, and most high-impact papers from China are related to nanotechnology.

In terms of biosensing translation, application, and market development, China started later than Europe, America, and Japan. Notable successes include: the series of enzyme electrodes from the Shandong Academy of Sciences, which have been widely applied in China's food fermentation industry with over 90% market share; domestic blood glucose meter products such as Sinocare and Yicheng have entered the top ten sales brands in the domestic market; CapitalBio's gene chips have gained certain market share in disease detection. Overall, however, the international biosensing and biochip markets remain dominated by multinational corporations from other countries.

Therefore, to further enhance its influence in biosensing, China needs a two-pronged approach: first, consolidate existing achievements to achieve academic excellence and innovation leadership; second, emphasize translational research and collaborate with industry to make greater strides in global market development.

Current Research Hotspots and Technical Challenges

Wearable Biosensors and Non-Invasive Measurement Wearable sensor systems can generate individual vital parameters in real time, which holds significance in two aspects. First, at the micro level, real-time measurement of disease biomarker parameters and transmission of data to medical centers via mobile phones and other devices facilitates home care, personalized medicine, and telemedicine for patients. Second, at the macro level, as big data, cloud computing, Internet of Things, and other technologies converge with the internet, new technologies and business models are ushering disease prevention, diagnosis, treatment, and control into an intelligent era. Biosensing and physiological sensing systems connected to mobile phones as intelligent terminals will become an irreplaceable data source for health and medical big data. By receiving, storing, managing, and analyzing this data, public health status and disease patterns can be summarized and analyzed to provide better disease prevention and control strategies.

Currently, wearable sensor systems for physiological indicators such as body temperature, pulse, blood pressure, and respiratory rate have begun to gain popularity. These indicators can be directly measured using physical sensors. However, biosensors measure targets within the body, making non-invasive measurement the primary challenge. Human biochemical, immunological parameters, and disease biomarkers generally require blood collection. For metabolic indicators requiring daily monitoring, such as blood glucose, daily blood sampling represents a significant psychological and physiological burden, causing most patients to abandon routine monitoring due to fear of blood collection. Minimally invasive detection technology combining micro-sampling devices with highly sensitive biosensors can effectively reduce patient discomfort, but non-invasive measurement technologies remain under exploration. Two main technical pathways exist: electrochemical enzyme electrode methods and optical methods.

3.1.1 Enzyme Electrode Methods Since enzyme electrode methods struggle with percutaneous determination, researchers have attempted to indirectly reflect blood composition by measuring other body fluid samples [13]. For example, some use iontophoresis or negative pressure to induce glucose exudation from subcutaneous tissue for enzyme electrode measurement; Google and Novartis have collaborated to print micro-enzyme electrodes on contact lenses to measure tear glucose; the University of California is developing wearable enzyme electrodes that can measure biochemical components in sweat. In addition to overcoming respective technical challenges, indirect methods face major scien-

tific questions regarding the correlation and physiological significance between measurement results and corresponding substance concentrations in blood, requiring extensive basic and clinical research. Scholars at Huazhong Agricultural University recently used mass spectrometry to analyze biochemical components in sweat exosomes, helping identify suitable health or disease detection indicators in sweat [14].

3.1.2 Optical Methods Optical methods utilize the spectroscopic characteristics of detection targets, including elastic light scattering, Raman spectroscopy, and in situ SPR. Near-infrared spectroscopy for blood glucose measurement has been extensively studied. Glucose molecules have absorption peaks in the near-infrared region, but these overlap with absorptions from water, fat, and hemoglobin, causing severe interference. Additionally, light absorption and scattering by skin tissue significantly weaken the already weak glucose absorption signal. Moreover, skin and tissue thickness and structure vary among individuals, requiring personalized modeling for accurate results.

Two Israeli companies have developed “learning-based” blood glucose measurement technologies through big data modeling and machine learning. CNOGA’s TensorTip CoG device features four LED light sources emitting wavelengths of 600–1150 nm. As light passes through the finger, absorption by human tissue changes the transmitted light’s color, which is detected by an image sensor. Simultaneous blood glucose measurements establish correlations between glucose concentration and spectral changes. Through iterative learning and processor algorithms analyzing up to hundreds of millions of color combinations, the device can finally calculate blood glucose concentration non-invasively. Another product, GlucoTrack, employs a multimodal approach, measuring changes in ultrasound, electromagnetic waves, and heat at the earlobe to calculate glucose concentration. Since blood biochemical marker concentrations are generally very low, and biological factors such as skin thickness and tissue structure vary among individuals, learning and modeling must account for individual differences [15], which may increase the difficulty of popularization.

Raman spectroscopy is an inelastic scattering modality where scattered light wavelengths differ from incident light wavelengths, with effects arising from molecular vibration and rotation. Scientists have obtained Raman spectral characterization data and fingerprint libraries for various compounds. Since water molecules exhibit extremely weak Raman scattering, Raman spectroscopy is suitable for label-free determination of organic molecules in aqueous solutions. Numerous reports have described in vitro measurement of glucose, urinary glucose, albumin, etc., using Raman spectroscopy, and in vivo blood component measurement has become a current research hotspot [16]. However, like mid-infrared and near-infrared spectroscopy, Raman spectroscopy suffers from weak characteristic signals and high noise in percutaneous measurement, affecting accuracy and sensitivity. Moreover, the instruments are expensive, making practical application difficult. Surface-enhanced Raman spectroscopy (SERS) can

selectively amplify vibrations of specific chromophores in target biomolecules, greatly improving detection sensitivity. However, how to apply this method in vivo remains under exploration.

Biosensors and In Vivo Detection

Biosensors hold significant importance for in vivo detection, such as neural activity tracing, in vivo identification of tumor targets, and measurement of disease or health biomarker concentrations. Due to the complexity of the in vivo environment, biosensors face special requirements, with major challenges including interference from the in vivo environment and non-specific components, miniaturization of detection devices, and non-invasive measurement.

Neurotransmitters (e.g., dopamine) are signals secreted and transmitted by nerve cells to target cells, regulating human behavior and brain function. Abnormal biosynthesis and metabolic transformation of neurotransmitters lead to severe diseases. Dopaminergic neurotransmission plays a major role in motivation, learning, cognition, and motor regulation, and its level abnormalities are associated with addictive behaviors, neurological diseases (such as Parkinson's, Alzheimer's, and Huntington's diseases), schizophrenia, and psychosis [17]. Three methods exist for in vivo dopamine measurement: (1) Microdialysis sampling combined with electrochemical analysis, a minimally invasive method with approximately 20-minute time lag. (2) Positron emission tomography (PET), a non-invasive method but with expensive equipment and long duration (over 40 minutes). (3) Fluorescence fiber photometry, requiring implantation, a minimally invasive method with real-time measurement. Since dopamine itself is an electroactive substance, electrochemical analysis is currently the mainstream technology. Related biosensors include enzyme electrodes [18], DNA-modified electrodes [19], aptamer-modified electrodes [20], and molecularly imprinted polymer (MIP)-modified electrodes [21]. Nanomaterials can further enable minimally invasive analysis [22], with high spatiotemporal resolution and anti-interference against electroactive substances being primary research objectives.

Other reported in vivo detection and tracing targets include NO (a free radical signaling molecule) [23] and ethanol and acetaldehyde (neuroactive agents) [24].

Optogenetic technology may also be applied to develop biosensors for in vivo detection. In G protein-coupled receptor (GPCR) signaling processes modulated by neural activity, various types of molecular photoreceptors can participate, such as opsins, photoactive proteins, photoswitch molecules, and fluorescent proteins. These may be natural or genetically engineered. Molecular photoreceptors undergo conformational changes upon external excitation, triggering GPCR signaling pathways. Through photoactivation and deactivation, cellular signal modulation is achieved [25], enabling monitoring of neural activity in vivo. Such photoreceptors can be classified as molecular biosensors.

Molecular Biosensing and Cellular Molecular Imaging

Molecular biosensors are sensors constructed from biological macromolecules such as DNA or proteins through genetic recombination or DNA synthesis techniques, particularly suitable for detecting intracellular molecular events. Currently, four major types of molecular sensors are widely used: molecular beacons (MB) [26], fluorescence resonance energy transfer (FRET) systems [27], bioluminescence resonance energy transfer (BRET) systems [28], and bimolecular fluorescence complementation (BiFC) systems [29]. Through their own conformational changes, photoreactions, and optical activity variations, they indicate the localization, movement, and distribution of target biomolecules in living cells, molecular interactions, conformational changes, enzyme activity detection, and cellular and subcellular responses to environmental changes and exogenous compounds [30]. Combining molecular biosensors with super-resolution microscopy enables imaging detection of single-molecule events [31], which is beyond the reach of traditional biosensors and holds great significance for life science research. Currently, super-resolution imaging is performed on fixed cells, and the resolution for molecular event detection in living cells has just broken the microscope diffraction limit (200 nm). Achieving ultra-high spatiotemporal resolution molecular event detection in living cells remains a challenge.

Online Monitoring in Bioreaction Engineering Processes

Bioreaction engineering refers to industrial processes that produce chemicals, pharmaceuticals, or food through large-scale cultivation of microorganisms, plant, or animal cells. Process automation is crucial for improving productivity and energy conservation. While detection and control of physical and chemical parameters have been achieved, online monitoring of biological parameters such as biomass, metabolites, substrates, and products remains challenging. The main obstacle is that biological elements cannot withstand the high-temperature, high-pressure sterilization environment inside bioreactors. Current monitoring methods involve sampling from bioreactors during production (so-called “offline analysis”) or diverted analysis through filters. Additionally, detection of microbial intermediate metabolites is difficult due to the lack of suitable enzyme electrodes. Drawing on synthetic biology approaches to construct cascade enzyme sensors or whole-cell metabolic biosensing systems may solve this problem [32]. Online monitoring of biological parameters is the final barrier to achieving full-process automation in bioreaction engineering and urgently needs to be overcome.

Biosensors and Field Monitoring

Biosensing equipment is highly suitable for field applications due to its portability and rapid measurement. Application scenarios include: measurement of water, soil, and atmospheric environmental indicators (organic compounds, heavy metals, etc.); monitoring of process control indicators in wastewater treatment; farmland fertility testing; on-site detection of food components, additives, and

contaminants; field detection for bioterrorism countermeasures; border quarantine and detection of prohibited compounds; biological and environmental indicator monitoring in special environments (such as aerospace, deep-sea, and polar regions); and bedside point-of-care testing (POCT) monitoring for critically ill patients. As people's quality of life improves, related demands are growing increasingly strong.

Stability of Biosensing Elements

Poor stability of biosensing elements remains the most significant limiting factor for their widespread application. Currently, several solutions exist: (1) improving stability of biological elements through molecular evolution or protein engineering methods; (2) selecting cellular elements from extremophiles, which typically exhibit good stability, as biosensing recognition elements; (3) adding stabilizers and protectants during storage of biological recognition elements to extend shelf life; (4) replacing natural enzymes with artificial enzymes or molecular imprinting technology [33,34], which have excellent stability but require improved catalytic activity; (5) using aptamers, which have better stability than protein molecules and have replaced antibodies as molecular recognition elements in some applications [35,36]; and (6) utilizing the enzyme-mimicking effects of inorganic nanomaterials to replace natural enzymes (primarily peroxidases), an innovative contribution by Chinese scholars [37].

Conclusion: Leveraging One-Health and Interdisciplinary Integration to Achieve Excellence and Leadership in Biosensing Research for Social Benefit

In China, with economic development and rapidly improving living standards, changes in lifestyle and work patterns have significantly altered the disease spectrum. Chronic diseases such as metabolic disorders, cancer, and cardiovascular diseases have become the major disease burden. Additionally, sub-health issues, food safety concerns, and environmental sanitation problems have attracted widespread societal attention. In response, the state has promulgated the "Healthy China 2030" Planning Outline, elevating Healthy China to a national strategy that drives the One-Health concept from theory to implementation, thereby providing new momentum for biosensing research. With its many characteristics—including speed, accuracy, and portability—biosensing can play a unique role in chronic disease monitoring and management, POCT, telemedicine and personalized medicine, food safety and environmental pollution monitoring. Therefore, it is recommended that relevant national programs and special projects give high priority and strengthen support.

The continuous 50-year development of biosensing has benefited from the interdisciplinary integration of life sciences, physics, chemistry, materials science, and information technology. Today, to meet the demands of One-Health development, biosensing research still faces a series of challenges. In this new era, the development and integration of emerging disciplines such as synthetic bi-

ology, artificial intelligence, nanotechnology, and big data may generate new ideas, principles, and methods, promoting solutions to technical challenges in biosensing and enhancing performance while endowing it with new functions and characteristics. Chinese biosensing research will leverage the external momentum of One-Health development and the internal momentum of emerging and interdisciplinary development to achieve academic excellence and leadership, ultimately benefiting society.

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