MINI-REVIEW

State of the art in development of molecularly imprinted biosensors

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Abstract
Biosensors are a class of smart devices fabricated for target analyte detection. A biosensor is commonly made of three basic components: a specific bioreceptor, a physicochemical transducer, and a signal processing device. The bioreceptor part features one of the more crucial technologies of a biosensor to perform specific detection of analytes. They commonly make use of various molecular recognition elements, such as enzymes, natural receptors, antibodies, nucleic acid aptamers, and even synthetic receptors. Then, the molecular recognition events of these bioreceptors can be translated into readable signals in various forms like electrochemical, optical, piezo/pyro electric, etc. Finally, these signals are mathematically processed for quantitative analysis. Nowadays, the great advances in biomimetic materials, in particular the synthetic receptors based on molecularly imprinted polymers (MIPs), promote tremendous development of biosensors. Integration of this field with artificial intelligence enables emerging design of advanced biosensors, which has moved from concept to implementation, meanwhile facing new opportunities and challenges. With no doubt, bioreceptor innovation based on molecular imprinting is an emerging driving force for biosensors development. In this review paper, we provide an overview of MIP-based biosensors, and also their challenges and opportunities moving forward toward wearable devices are discussed.

KEYWORDS
biosensors, molecularly imprinted polymers, plastic antibodies, smart wear, synthetic receptors

1 | INTRODUCTION

Bioassays, which are often fabricated for accurate identification and efficient quantification of target analyte, have received constant attention from all walks of life for a long time.² Owing to the rapid development in molecular biology, material science, and mechanical engineering, a new device (so-called biosensor) that can translate the molecular recognition event into a read-out signal for various applications, such as clinical diagnosis, food safety and environmental monitoring, and anti-terrorism detection, has emerged in recent years.² The quantifiable and exclusive signal reported by a biosensor reflects the type and concentration of target analyte.³ The first biosensor was reported by Clark and Lyons in 1962, which was successfully applied...
for glucose detection with the assistance of glucose oxidase.  

As shown in Figure 1, a biosensor is an integrated device for measuring specific bio/chemical reactions based on bioreceptors (e.g., enzymes, natural antibodies, 3D nucleic acids-based aptamer, etc.), which provides signal outputs (e.g., electrochemical signals, optical signals, piezo/pyro electric signals, etc.) to reflect target analyte information. A biosensor is usually composed of three basic elements: a receptor for specific recognition, a physicochemical transducer for signal translation, and an analysis device for signal processing. Specifically, the receptor is made of a molecular recognition system that can identify the target analyte with a high degree of selectivity. The transducer (detector) transfers molecular recognition events to a readable signal with a high degree of sensitivity. Nowadays, signal processing devices are no longer cumbersome computers, but are smartphone apps, which bring smart biosensors due to the development of information technology.

Due to the limitation of biological receptors (like the issue of instability and high price, as well as the concern of batch-to-batch viability), a tailor-made chemical receptor, which is a molecularly imprinted polymer (MIP) that can specifically identify and bind toward target molecules, has come into the spotlight for the design of biosensors. Owing to synthesis technology progress that results in excellent biocompatible MIPs, these biomimetic antibodies have found favor for in vitro and in vivo biosensing. The MIP-based biosensors are rapid and on-site, which has answered many questions in medical diagnostics, food safety, environmental monitoring, process control, etc. If this type of biosensor uses information technology to further improve its performance by conducting pattern recognition and big data analysis, it is expected to achieve a broader application prospect and contribute to the global health care. In this paper, we report how MIPs are designed as superior biomimetic antibodies for biosensor development, with respect to aptamers and antibodies. Meanwhile, some advanced MIP-based biosensors will be presented, so as to point out the challenges and opportunities of biosensors in future wearable devices.
FIGURE 2  Schematic representation of MIP synthesis process. 1: Functional monomers, 2: cross-linking monomers, 3: template molecule. (A) Auto-assembly of the monomer-template complex. (B) Polymerization. (C) Removal of the template. Reproduced with permission.\textsuperscript{15} Copyright 2002, Royal Society of Chemistry

| Parameters                        | Antibodies | Aptamers | MIPs          |
|----------------------------------|------------|----------|---------------|
| Production                       | Animal host, months | SELEX, hours to weeks | 2–3 days      |
| Affinity                         | $10^{-7}$ to $10^{-13}$ M | $10^{-9}$ to $10^{-12}$ M | $10^{-3}$ to $10^{-10}$ M |
| Anti-interference (selectivity)  | Very selective | Highly specific | Family selective |
| Stability                         | Narrow temperature and pH range | Wide ranges of pH, temperature, and ionic strength | Wide temperature and pH range |
| Storage time                     | Limited | Stable many years in $-20^\circ$C | Stable over many years |
| Cost                             | £100 approx for microgram quantities | £1–10 approx per OD | £10 for gram quantities |
| Reusability                      | Not usually | Renewable | 100s of times |
| Designability                    | Not designable | DNA library | Rational designed |

2 MOLECULARLY IMPRINTED POLYMERS

People have in the past learned from nature and have used nature’s design rules as an inspiration in advancing bio-compatible materials and creating higher ordered systems.\textsuperscript{13} Taking lessons from biology, the new generation of biomimetics is focused on engineering self-assembled, hydride, functional materials, using proteins’ unique and specific interactions with all kinds of organic or inorganic molecules.\textsuperscript{14} With the successful use of self- and co-assembly principle and advance in materials science based on molecular and nanoscale recognition, biomimetics is now entering molecular scale! The most popular research topics about nature principle studies include: specific recognition, self- and co-assembly into highly organized hierarchic structures, etc. Inspired by all these mechanisms mentioned above, two kinds of biomimetic receptor synthesis recently attracted a lot of attention in all areas. During the synthesis process, biologists prefer to use natural monomers, like nucleotide (involving adenine, cytosine, guanine, thymine, uracil) to synthesize aptamers, or 21 kinds of amino acids to synthesize artificial proteins (such as abzymes, affimers, etc.). In the interdisciplinary study of biology, chemistry, and physics, people are keen on using modified biological components, for example, amino acids adapted polymerizable monomers, which are widely used for MIPs synthesis.\textsuperscript{8,9}

As shown in Figure 2, MIP is constructed by the functional and cross-linking monomers in the presence of a molecular template (i.e., the target molecule or a derivative thereof).\textsuperscript{15} First, the functional monomers autoassemble with the template. After copolymerization with cross-linking monomers, the monomer-template assembly is held in position by the highly cross-linked 3D structure. Subsequent extraction of template leaves specific sites with a size, shape, and chemical functionality complementary to the target molecule. As a result, the synthesized MIP is capable of selectively recognizing and binding the target molecules even in real samples.

As summarized in Table 1, some key features of bio(mimetic) receptors, including nature antibodies, aptamers, and MIPs, are analyzed. Comparing with natural monomer-composed receptors, MIPs exhibit very impressive advantages: no animal killing, stable in a complex environment over years, low cost, reusable, and designable, while maintaining the comparable affinity and acceptable anti-interference performance. Therefore, the MIPs are more promising identification components for biosensor fabrication.\textsuperscript{16}
2.1 Obtained optimization

From the perspective of materials science, to optimize the detection performance of MIP-based biosensors, rational design of the molecular recognition sites by imitating natural antibodies plays an important role. Moreover, we can also combine MIPs with biomolecules, such as aptamer-incorporated MIPs, so as to improve the selectivity. Recently, Professor Liu’s research group proposed the concept of precise imprinting strategy for the facile preparation of specific MIPs (Figure 3A). First, a glycoprotein was immobilized on a boronate affinity substrate. Then, an in situ dual enzymatic digestion created the glycopeptides with desirable peptide length by using trypsin and pronase E, respectively. Toward the desirable glycopeptide, a thin layer MIP was generated to cover the glycopeptides to an appropriate thickness. This precise-imprinting approach was proved to be widely applicable for two kinds of glycoproteins, those containing only N-glycans and both N- and O-glycans. Using the MIPs with excellent glycan specificity (particularly for O-glycans), specific extraction of glycopeptides and
glycoproteins containing certain glycans from complex samples was successfully achieved, indicating a great potential in glycan-related applications and research.

Moreover, another MIP-based fluorescence sensor (MIFS) was developed for glycoprotein detection by using nanoparticle decomposition promoted signal amplification (Figure 2B). Horseradish peroxidase (HRP), which was immobilized on the boronic acid modified magnetic nanoparticles (MNP), was used as a model target. After the synthesis of capture, a boronic acid modified tetra(4-carboxyphenyl) porphyrin nanoparticles (BA-TCPP NPs) were also generated as signal tag. During detection process, the BA-TCPP NPs were captured by MIPs in the presence of HRP. Then, the BA-TCPP NPs could be dissolved into thousands of porphyrin molecules by adding NaOH, which resulted in amplified fluorescence signal. In this work, the synthesized MIFS were successfully used for the detection of HRP in the linear range of 0.1 μg/L to 10 mg/L, with a limit of detection (LOD) of 0.042 μg/L (S/N = 3).

2.2 | Remained challenges

In the 21st century, the biosensors featured with wearable and intelligent properties are being introduced. The smart wearable biosensors provide opportunities for continuous monitoring of target biomarkers in human bodies. Despite of great effort in wearable biosensors development, there still remain a lot of challenging problems. The wearable biosensors are promising for making real-time clinical interventions in pathological conditions, which brings key information for preventing pathological conditions from becoming life-threatening events or chronic conditions. Thus, there is no doubt that the development of wearable biosensors is of great advanced significance for real-time monitoring of diseases and providing clinical intervention programs. However, only the invasive glucose monitoring biosensors have been commercially available till now. Thus, challenges to overcome MIP-based wearable biosensors fabrication should be taken seriously.

The wearable biosensors designed for tracking biomarkers should function well for a long time. Because of the limited number of binding sites, the biosensor is impossible to report further changes once saturated with target analyte, as the analyte—receptor interactions are usually irreversible. To overcome this challenge, the designed biosensor should be refreshable.

Because the components in the real environment are complex and dynamically variable, direct detection of low-abundance molecules is a challenging problem. The non-enzymatic amplification technology based on DNA cascade reaction is a commonly used signal amplification method in biosensing. However, as the reaction kinetics process relies on the spontaneous diffusion and random collisions of nucleic acid probe molecules, the reaction may last hours. On the other hand, nanoparticles decomposition-triggered signal amplification needs extreme stimuli which is impossible to happen in normal physiological environment. To overcome this challenge, the designed biosensor must be signal amplifiable.

3 | APPLICATIONS OF MIP-BASED BIOSENSORS

Currently, MIP-based biosensors are receiving immense attention. They are accurate and stable analytical methods to guarantee biomedical analysis quality, environmental monitoring timeliness, food safety standards, as well as anti-terrorism urgency (Figure 4).

3.1 | Electrochemical biosensors

Electrochemical biosensors have made a significant impact on the global market, which is attracted by their excellent sensitivity. A conventional electrochemical sensing process relies on the electro-active molecules attached onto the electrode. Thus, traditional
electrochemical biosensors always suffer from interferences in real samples due to the instability of bioreceptors. To avoid interferences, some essential functional materials were applied onto the sensing interface. However, nonspecific adsorption remains a problem.\(^{31}\) Therefore, the receptor-sensing interface construction is very crucial,\(^{32}\) so as to facilitate effective electron.\(^{33,34}\) Another inevitable problem comes from the irreversible property of receptor–analyte interactions, which makes it difficult to maintain good performance,\(^{35,36}\) leading to heavily discounted sensitivity and stability (reproducibility). Therefore, traditional electrochemical biosensors face inherent limitations and are difficult to meet the needs of practical applications.\(^{37,38}\) On the other hand, MIP-based electrochemical sensors show great advantages, especially in sensitivity and stability.\(^{39–47}\)

To show an increased sensitivity of MIP-based electrochemical biosensor, an example of MIP-coated gate field-effect transistor (FET) biosensor was reported for low-concentration glucose detection in biological fluid samples in an enzyme-free manner (Figure 5A).\(^{48}\) The glucose was incorporated in MIP (GluMIP) by binding to vinylphenylboronic acid (PBA), which led to density change in terms of molecular charges. Thus, the GluMIP-coated gate FET sensor may detect target analyte as long as molecular recognition events cause intrinsic changes in the density of molecular charges. To this end, the GluMIP-coated gate FET sensor provided an output voltage change as a result, showing LOD of 3 \(\mu\)M and a linear range of 100 \(\mu\)M to 4 mM glucose. Moreover, this sensor shows an approximately 200-fold higher selectivity for glucose than for fructose due to PBA’s preference.

To show the excellent stability of MIP-based electrochemical biosensor, an example of microfluidic paper-based biosensor was reported for ultrasensitive detection of ovalbumin (OVA) (Figure 5B).\(^{49}\) During the fabrication,
Au nanorods with a large surface area and superior conductivity grew on the paper and immobilized OVA via boronic acid. Then, the MIPs were synthesized by using 4-mercaptophenylboronic acid (MPBA), so as to capture OVA. For detection process, SiO$_2$@Au nanocomposites labeled MPBA and cerium dioxide (CeO$_2$)-modified nicked DNA double-strand polymers (SiO$_2$@Au/dsDNA/CeO$_2$) were used as signal tag, which could be captured onto the surface of the paper in the presence of OVA. An electrochemical signal was generated by using nanoceria as redox-active catalytic amplifiers in the presence of 1-naphthol in electrochemical assays. As a result, the MIP-based electrochemical biosensors could be applied in the detection of OVA in a linear range of 1 pg/ml to 1000 ng/ml with LOD of 0.87 pg/ml ($S/N = 3$), demonstrating the great potential in clinical diagnosis and other related fields.

### 3.2 Optical biosensors

Optical sensors can be a simple component for measuring light levels, or a highly sensitive device for detecting single photons. The most common optical sensors include fluorescence sensors, surface plasmon resonance (SPR) sensors, surface-enhanced Raman scattering (SERS) sensors, etc. Nowadays, the optical sensors have been developed to give dual-signal for multitarget detection, connected to a smartphone for real-time and in vivo monitoring, thus showing a huge application prospect.

SPR is a label-free sensing method, which may report kinetic information on molecular interaction without using chemical labeling/tagging. As a gold standard, the classical SPR sensor interrogates refractive index changes within a thin interfacial layer at a gold/dielectric interface, featured with advantages like high sensitivity (1 pg/mm$^2$)$^2$ and relatively short turnaround times for retrieving kinetics information. Based on SPR, localized SPR (LSPR) using metallic nanoparticles shows a bigger prospect. The LSPR sensors are compatible with advanced microfluidic architecture, which can reduce the complexity and miniaturization of optical systems. Therefore, they have been successfully applied to real-time diagnostic systems and integrated with microfluidics for high-throughput testing. Recently, Hu and coworkers synthesized sol–gel MIPs on Au nanorods toward three target proteins for the purpose of investigating the role of aromatic interactions in molecular recognition capability (Figure 6A). They found that the sol–gel MIPs with aromatic functionality exhibited an excellent, protein-dependent, improved sensitivity toward proteins with higher aromatic amino acid content. It is worth noting that aromatic interactions did not reduce the specificity of their MIPs. These results clearly show that the sensitivity of LSPR sensors can be enhanced by rational selection of functional monomers, making the LSPR sensing technology closer to practical applications.

In recent years, plasmonics has brought new revolutionary methods for analytes detection. SERS exploits the giant electromagnetic field enhancement provided by LSPR, allowing to tailor the molecular sensitivity to the atto-molar range and reach single molecule sensitivity. Xing and coworkers developed a new MIP-based sandwich assay called duMIP-PISA, in which both the target-capturing probes and the labeling nanotags were MIPs (Figure 6B). To achieve facile and efficient imprinting, some terminal epitope peptides were employed in this work. Compared with the single recognition based on one MIP, the duMIP-PISA exhibited higher specificity owning to the dual recognition effect. Practical application results demonstrated that the duMIP-PISA can measure neuron-specific enolase (NSE) in serum samples from healthy individuals and cancer patients. Compared with traditional immunoassays, duMIP-PISA has significant advantages, such as low cost, good stability, high speed, low sample consumption, and wide detection range. Therefore, we foresee that this method may be a promising tool for many important applications, such as disease diagnosis, biochemical research, and signal pathway research.

### 3.3 Color biosensors

To meet the increasing demand for simple, accurate, stable, and low-cost biosensors, development of the next-generation biosensing system for analyte detection in real samples remains challenging. Structural color sensor has recently become a frontier topic due to the advantages of chemical stability, vivid coloration, and anti-discoloration. As shown in Figure 7A, a stretchable, diffractive, color-based wireless strain sensor was fabricated for measuring strain. The color sensor worked by using an array of cone-shaped nanostructures on the surface of an elastomeric substrate under entire visible spectrum. When the substrate was stretched or compressed, the diffractive color was tuned according to the changing grating pitch.

The research of MIP-based color biosensors is still in the infancy stage, only one successful example based on structural color is given. As shown in Figure 7B, molecular imprinted structural color contact lenses were fabricated for sustained timolol release monitoring by self-reporting color change. When MIP bound to the target timolol, the lens reflected a green color. During the accumulative release of timolol, the lens presented a remarkable blue shift as structural color. This shows that the MIP-based color biosensors are promising for
monitoring controlled release of drugs, providing a great potential for functional biomaterial preparation.

### 3.4 Wearable biosensor

With the development of artificial intelligence and intelligent manufacturing technology, we predict that smart wearable and implantable biosensors will be an indispensable family doctor in people’s lives in future. These biosensors should allow more intimate contact with human bodies, so as to provide advanced health monitoring, disease detection, medical therapies, and human–machine interfacing. Regrettably, traditional electronics are not compatible with human bodies, as they are rigid, nondegradable, and cannot self-repair, while the human body is soft, dynamic, stretchable, biodegradable, and self-healing. In this regard, the top priority is to develop flexible electronic materials with fascinating performance in stretchability, biodegradability, and self-healing. Coincidentally, smart wearable and implantable biosensors based on MIPs were almost nonexistent until 2020.
shown in Figure 8A, a wearable MIP-based electrochemical biosensor was developed by using the screen-printed electrode, which was then successfully applied for noninvasive monitoring of lactate in the human sweat. First, Ag nanowires (AgNWs) were coated on the electrode. Then, MIPs were synthesized in the presence of lactate by using huge amount of 3-aminophenylboronic acid (3-APBA) on the electrode. As a result, the MIPs-AgNWs biosensor revealed high sensitivity and specificity for measuring lactate concentration ranging from $10^{-6}$ to 0.1 M, with LOD of 0.22 μM. Moreover, the sensor presented high stability with a recovery of 99.8% ± 1.7% during 7 months, a stable electrochemical response after been bended and twisted 200 times. Afterward, volunteers tested the sensor on the skin for in vivo noninvasive tracking of the perspiration lactate. The results bring us a ray of hope that wearable electrochemical biosensors based on MIP will be available in the near future, which exhibit
great potential in various applications, such as for human sweat evaluation in the military, physical examination of athletes, disease analysis, tissue repair, etc.

As the development of MIP-based wearable biosensors is still in the infancy stage, there is still a long way to go to achieve signal analysis based on artificial intelligence. But inspired from other fields, smartphones and wireless network-based analysis systems are promising to integrate with our biosensors. Recently, Lee and coworkers developed a phage-based color sensor and corresponding pattern recognition sensing system (Figure 8B). Their system needs a populated database as a reference for new data analysis. Upon capturing a new image, its RGB colorimetric information was then recorded and results were looked up in the database for calculations. The algorithm automatically determined the two closest records in the database and estimated the analyte concentration by interpolation with known values. Very conveniently, the obtained results could be shared across a wide range of electronic communication equipment. For example, they developed an automatic notification system for users to send out an SMS text message and an email of the sensing results. Moreover, their system could also post the results onto social media platforms and incorporate temporal information in addition to spatial data derived from Google Maps. Inspired by this work, we believe that more and more MIP workers will devote themselves to the development of smart biosensors.
4 | CONCLUSION

During the last decade, biosensing has witnessed rapid development in both sensing materials and analytical techniques. The development of new biosensors is faster than expected, owing to biomimetic nanotechnology. Using the MIP, a so-called artificial antibody, the interaction between the biomimetic receptor and the target analyte can be more favorable, leading to excellent sensitivity and stability. Moreover, the MIP-based biosensors are easy to design with multiple functionalities, and the output signal can be amplified upon nanoparticle decomposition. While more and more MIP-based biosensors are proposed, featured with significant accuracy, they can be feasibly applied for various applications such as environmental monitoring, medical diagnosis, food safety control, and anti-terrorism detection. Nowadays, the research on new principles, new materials, and new developments of sensing technology has become more in-depth and extensive. New varieties, new structures, and new applications of biosensors continue to emerge. Among them, the “five modernizations” have become an important trend during development, which are the intelligence, mobility, miniaturization, integration (multifunctional), and diversification. With the recent advancement of technology, the reduction of costs, and the improvement of performance and reliability, driven by the rapid development of the Internet of Things, mobile internet and high-end equipment manufacturing, the application market of MIP-based biosensors will develop brilliantly.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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