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Small-molecule biosensing: from bio-inspired recognition elements and sensor devices to AI-guided design

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Jin Wang received his Ph.D. in Biochemistry from the University of Tsukuba in 2015. He subsequently served as a Postdoctoral Fellow and Specially Appointed Assistant Professor at Kyushu University, with support from the JST ImPACT and JST CREST programs. In 2020, he joined Okayama University as an Assistant Professor and was promoted to Associate Professor in 2024. His current research focuses on the development of advanced biosensors for highly sensitive and selective small-molecule detection.

Abstract

Precise detection of small molecules—including neurotransmitters, hormones, pesticides, and environmental toxins—remains a fundamental challenge in chemical sensing and bioelectronics due to their low molecular weight, structural similarity, and limited intrinsic signal transduction. Bio-inspired molecular recognition strategies have therefore played an important role in enabling selective and sensitive small-molecule detection across diverse sensing platforms. This account summarizes the author's research trajectory on small-molecule biosensors, systematically covering the development of molecular recognition elements and their integration into electrochemical, plasmonic, fluorescence, and terahertz-based sensing devices. The work spans antibody-derived peptide recognition elements, enzyme-based microelectrochemical sensors for multiplex pesticide detection, peptide-based surface plasmon resonance sensors, fluorescence-based molecular probes, and DNA-aptamer-functionalized sensors for label-free, real-time detection. Collectively, these studies illustrate a coherent approach to sensor development that couples bio-inspired recognition with device engineering and signal transduction optimization. Building on these established bio-inspired methodologies, recent efforts have begun to explore the use of artificial intelligence (AI) and data-driven modeling as supportive tools for the design and optimization of molecular recognition elements. While these AI-guided strategies are still at an early, largely prospective stage, they highlight a potential transition from empirical discovery toward more predictive and scalable design paradigms. Together, this body of work highlights a transformative, AI-enabled framework for small-molecule biosensing, in which molecular recognition design, physics-based simulation, and biosensor engineering converge to enable predictive, self-adaptive, and accelerated discovery of next-generation sensing systems.

Keywords: AI-guided molecular recognition, recognition elements, small molecule biosensor.

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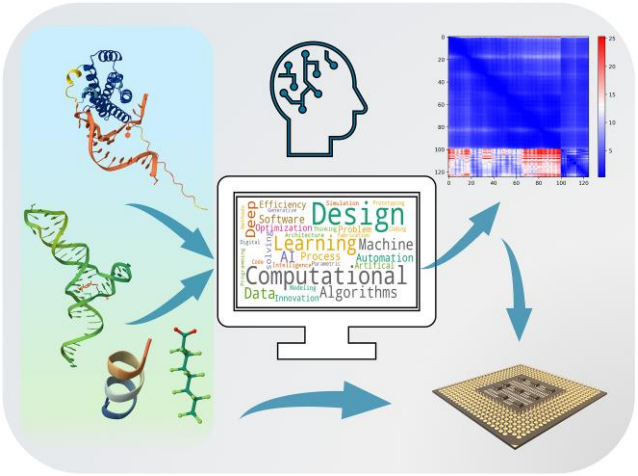
Graphical abstract



1. Introduction

Small molecules—such as neurotransmitters (eg dopamine, serotonin, acetylcholine, ATP), hormones (eg cortisol), metabolites (eg glucose, lactate), taste compounds, environmental pollutants (eg pesticides, per- and polyfluoroalkyl substances: PFAS), odorous volatile organic compounds (VOCs) and biogenic VOCs (BVOCs), and plant secondary metabolites (eg isoflavones), are important chemical markers across medicine, agriculture, environmental systems, and climate.[1–7] Their reliable detection underpins disease diagnosis, therapeutic monitoring, food safety, and environmental surveillance. However, their small molecular size, structural diversity, low abundance, and frequent charge neutrality make them challenging analytes for traditional assays such as enzyme-linked immunosorbent assays (ELISA) and high-performance liquid chromatography-mass spectrometry (HPLC-MS), which often require labeling, complex sample preparation, and benchtop instrumentation that limit temporal resolution and portability.

Recent biosensing advances—particularly optical/fluorescent, electrochemical, and novel material-based hybrid sensors—have enabled label-free, sensitive, and rapid small-molecule detection.[8–10] Continued development of aptamer-functionalized interfaces, protein-inspired recognition elements, and bioelectronic devices has significantly expanded the range of detectable analytes.[11–14] In parallel, emerging AI platforms including structure- and sequence-aware models, graph neural networks, artificial neural networks, and generative language models are accelerating rational engineering of proteins, aptamers, and peptides, promising unprecedented specificity, robustness, and tunability.[15–21]

This account summarizes recent progress in small-molecule biosensing with an emphasis on (i) bio-inspired recognition elements, (ii) AI-driven recognition design, and (iii) advanced sensor architectures. We compare sensing modalities, showcase applications ranging from neurotransmitters to plant metabolites, and discuss future directions in AI–guided strategies for molecular recognition.

2. Small molecules

Small molecules—typically defined as compounds with molecular weights below 1,000 Da—represent a chemically diverse class of analytes that serve as important chemical markers across biological, environmental, and technological systems. These include neurotransmitters such as dopamine and serotonin in blood, cerebrospinal fluid, and urine; stress hormones like cortisol detectable in sweat and saliva; metabolic intermediates such as glucose and lactate; VOCs; environmental pollutants including pesticides and per- and polyfluoroalkyl substances; and plant secondary metabolites such as isoflavones (Fig. 1). Their functional significance is broad: dopamine imbalance underlies neurological conditions such as Parkinson's disease and schizophrenia, cortisol fluctuations reflect stress physiology and can serve as biomarkers for metabolic or psychiatric disorders, and pollutants such as trinitrotoluene (TNT) and Per- and PFAS pose substantial risks to ecosystems and human health. Therefore, sensitive detection at trace levels is urgently needed.

Detecting small molecules remains substantially more challenging than targeting macromolecules such as proteins or nucleic acids. Small molecules lack multiple epitopes for antibody recognition, often exhibit low immunogenicity, and are typically present in picomolar concentrations in biofluids. Their structural similarity to endogenous metabolites complicates selective detection. Moreover, the availability of materials and biomaterials capable of selectively recognizing such a vast chemical space remains limited.

Traditional analytical techniques, including HPLC-MS, and ELISA, are indispensable for quantitative validation. However, they have intrinsic limitations:

1. Complex sample preparation and labeling introduce procedural delays and operational complexity.
2. Low temporal resolution hinders real-time monitoring of rapid molecular fluctuations.

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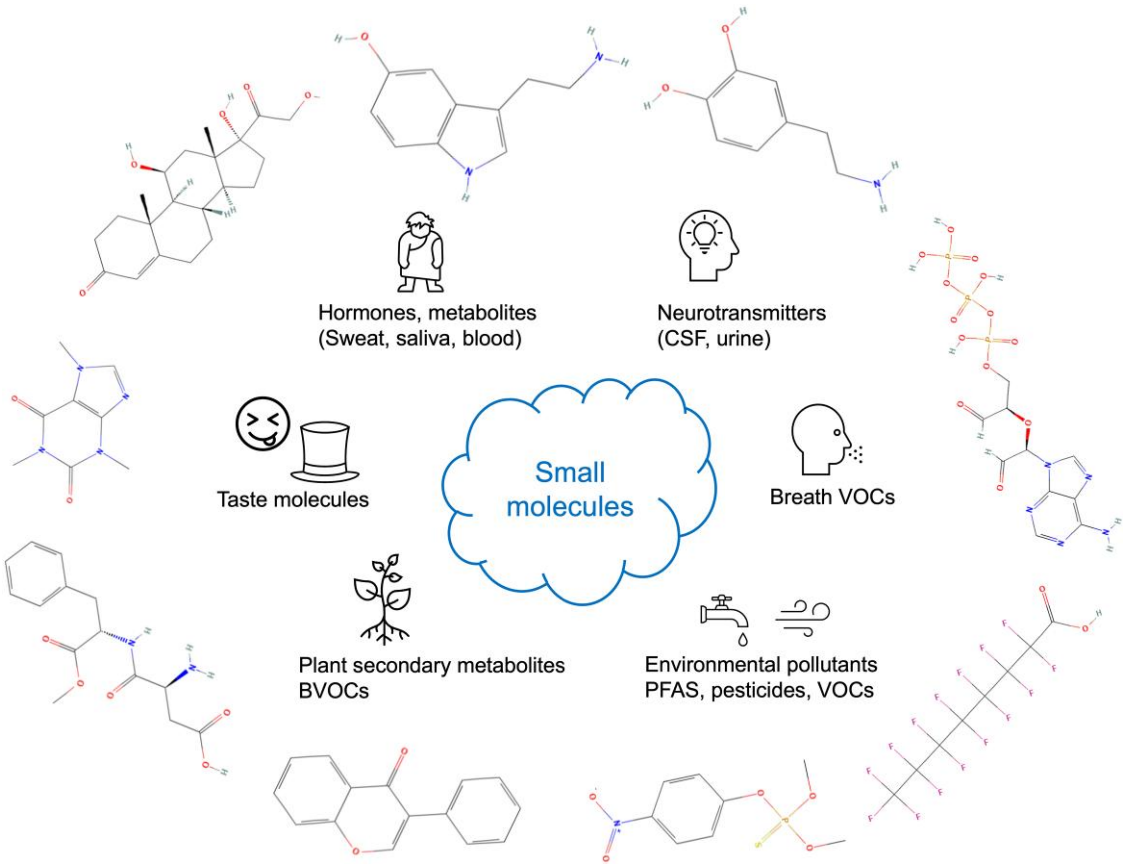

Fig. 1 Small molecules as ubiquitous chemical markers.

3. Dependence on bulky instrumentation and controlled environments limits portability and field deployment.
4. Poor selectivity for neutral or structurally similar compounds often requires chemical derivatization.

These constraints underscore the urgent need for innovative biosensing technologies with high sensitivity, molecular specificity, rapid response, and operational portability to enable next-generation small-molecule detection.

3. Bio-inspired recognition elements

The development of effective small-molecule biosensors relies heavily on recognition elements capable of interacting with targets selectively and sensitively. Bio-inspired recognition elements—derived from natural molecular systems such as antibodies, enzymes, peptides, and nucleic acids—form the basis of most modern sensing strategies. These elements mimic or repurpose biological mechanisms of molecular recognition, enabling integration into ELISA, electrochemical, microfluidics, optical, and photonic devices.

3.1 Antibodies

Monoclonal antibodies are among the most established recognition elements owing to their extraordinary specificity and affinity for target molecules.[17,22,23] Their widespread use in immunoassays, including ELISA, Förster resonance energy transfer, and lateral flow tests, demonstrates their robustness and efficiency in diagnostics.[17] However, their relatively large size, limited thermal stability, and high production cost can pose challenges for miniaturized biosensors for wide applications. For example, their large size often exceeds the Debye length (often several nanometers) in physiological conditions of electrochemical field-effect transistors, reducing sensitivity toward small molecules. Recent efforts have sought to engineer antibody fragments (eg Fab, scFv, and nanobodies) with improved stability and easier expression, thereby expanding their applicability in electrochemical and surface plasmon resonance (SPR) sensing platforms. Figure 2 presents representative structures of a monoclonal antibody, an anti-cortisol Fab fragment, a single-chain variable fragment (scFv) derived from an anti-TNT antibody, and a cortisol-binding nanobody with molecular weights ranging from hundreds to tens of kilodaltons (kDa). These recognition elements typically exhibit high binding affinities (in the nanomolar range) for specific target molecules; however, their production and purification can be complex, making rapid and efficient biosensor development challenging.

3.2 Enzymes and proteins

Enzymes offer catalytic amplification in biosensing by converting analyte recognition into measurable signals via substrate turnover. Typical examples include glucose oxidase in glucose sensors and acetylcholinesterase in pesticide detection.[24] Figure 3 shows the enzymatic reaction mechanism on a 3-electrode microelectrochemical sensor for sensitive pesticide detection, where pesticide-induced enzyme inhibition suppresses the electrochemical oxidation of the electroactive species hydrogen peroxide (H_2O_2).[7] For metabolic analytes,

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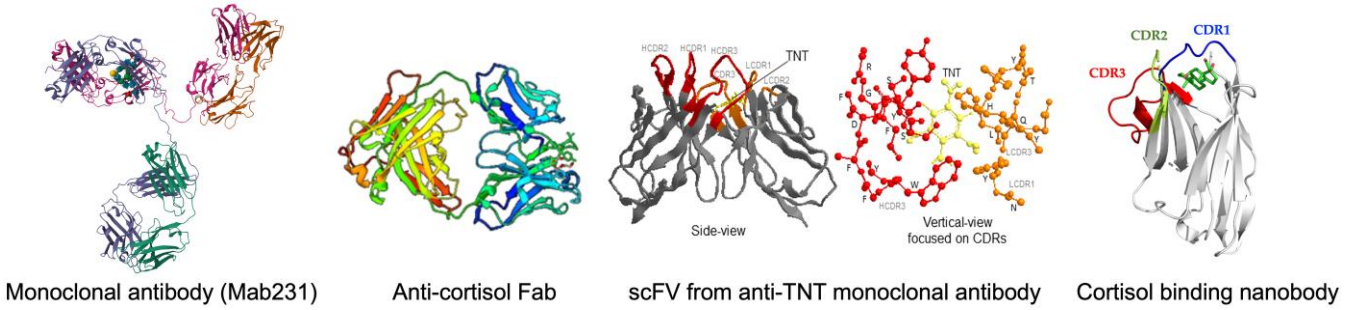

Fig. 2 Representative bioinspired recognition elements reconstructed from the RCSB Protein Data Bank (RCSB PDB) and ACS Combinatorial Science. Copyright (2017) American Chemical Society and RCSB PDB.

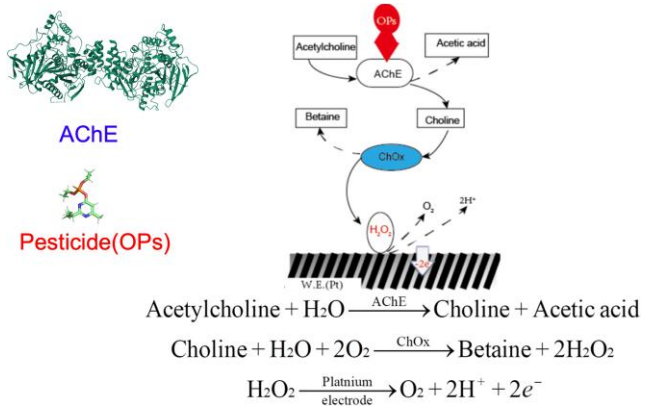

Fig. 3 Schematic of the enzyme-catalyzed reaction mechanism for pesticide detection via electrochemical sensing.[7] Copyright (2014) Elsevier.

enzyme-based sensors are highly effective, because redox reactions catalyzed by the enzyme generate measurable electron-transfer signals, enabling quantitative detection using electrochemical sensors.

Proteins, also known as functional natural recognition elements,[25,26] serve as specific binding receptors for various odorant VOCs. In biological olfactory systems, proteins such as odorant-binding proteins and olfactory receptors play a critical role in capturing and transporting hydrophobic odor molecules through the aqueous mucus layer to receptor sites.[3] Their high affinity and selectivity toward VOCs arises from shape complementarity, hydrophobic interactions, and hydrogen bonding. By exploiting these mechanisms, protein-based biosensors have been developed for detecting environmental VOCs with high sensitivity and selectivity, enabling applications in air-quality monitoring, food-freshness assessment, and medical diagnostics through breath analysis.

3.3 Peptides

Peptides derived from natural receptors (eg hormone-binding domains) or developed using phage displays and combinatorial libraries bridge the gap between antibodies and small organic ligands. Compared with antibodies, their smaller size enables faster binding kinetics and easier synthesis. Peptides have been successfully implemented in electrochemical, SPR, and near-infrared optical sensors. Their sequences can be rationally modified to optimize hydrophobic interactions, hydrogen bonding, or π–π stacking with specific small-molecule targets, enhancing both selectivity and sensor performance.[27–30] Figure 4a presents the rational design process for identifying TNT-binding peptide candidates derived from the antibody's complementarity-determining region (CDR). The heavy-chain CDR3 sequence comprising 14 amino acids was identified as the optimal TNT-binding peptide through combined computational visualization and subsequent experimental validation (Fig. 4b).[28] Figure 4c shows the 5 optimal structural conformations (one representative of each of the 5 best clusters) of the designed breath VOC-binding peptides generated using the PEP-FOLD algorithm, based on clustering reports. These peptide models were optimized for binding targets such as nonanal (the model optimized for the grand average of hydropathicity or GRAVY score) and benzaldehyde.[3]

3.4 DNA aptamers

DNA and RNA aptamers, often termed "chemical antibodies," represent a class of single-stranded synthetic oligonucleotides, typically ranging from 20 to 100 nucleotides in length. They are selected through a powerful in vitro selection technique called Systematic Evolution of Ligands by Exponential Enrichment (SELEX). SELEX allows researchers to select oligonucleotides that can fold into highly defined, stable 3-dimensional conformations capable of binding a diverse range of targets, spanning small molecules, ions, proteins, and even whole cells, with both high affinity and specificity, mimicking the molecular recognition capability of traditional protein antibodies.

The versatility of aptamers as recognition elements has led to their successful integration into a wide variety of biosensing platforms, particularly in the realm of small molecule and biomarker detection. Their target-induced conformational changes support highly sensitive electrochemical sensors and fluorescence probes, such as molecular beacons, and even advanced systems including Terahertz Chemical Microscopy (TCM).[31–35] Figure 5 shows a cortisol aptamer immobilized on a semiconductor substrate named silicon on sapphire (SOS), achieving highly sensitive and selective detection of the stress biomarker cortisol. Molecular docking simulations reveal the binding configurations of cortisol (Fig. 5a) and histamine/dopamine to the aptamer (Fig. 5i), which are further visualized through 3-dimensional and 2-dimensional representations of the cortisol–aptamer complex (Fig. 5b, c). The binding event is experimentally confirmed by UV–Vis absorption spectroscopy (Fig. 5d), while the sensing principle and surface functionalization of the SiO_2 substrate are presented schematically and morphologically (Fig. 5e, f). The spatial

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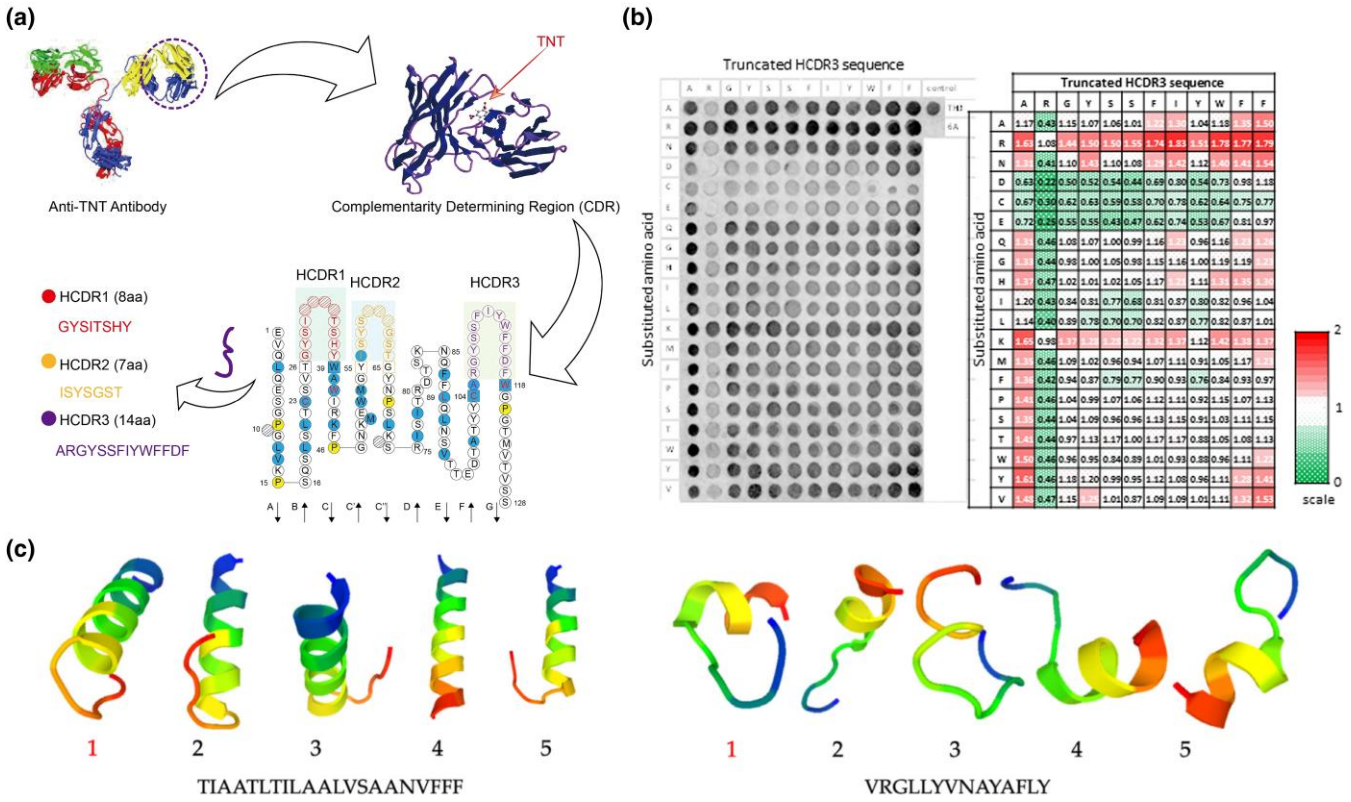

Fig. 4 (a) Rational design of the TNT binding peptide from the anti-TNT monoclonal antibody. Copyright (2018) Elsevier.[4] (b) Fluorescence truncated HCDR3 sequence evaluation Copyright (2017) American Chemical Society.[28] (c) Structural prediction of top breath VOC-binding peptides using PEP-FOLD.[3].

and quantitative sensing performance is demonstrated by differential terahertz amplitude mapping, calibration analysis, and selectivity evaluation against structurally related small molecules (Fig. 5g–h, j). Figure 6 presents AlphaFold-based structural predictions of the DNA aptamer–neurotransmitter complex in the presence of Mg^{2+} (Fig. 6a) and Ca^{2+} ions (Fig. 6b), together with the corresponding terahertz amplitude changes associated with ion-dependent binding interactions (Fig. 6c, d). These applications highlight the capacity of aptamers to enable label-free real-time detection with high sensitivity. While challenges remain in enhancing their stability and minimizing non-specific interactions within complex biological matrices such as blood or serum, the future of aptamer technology looks increasingly bright.

3.5 Other bio-inspired systems

Beyond antibodies, enzymes, peptides, and aptamers, several additional bioinspired recognition systems have expanded the biosensing toolbox. These emerging strategies are valuable for overcoming the limitations encountered in certain analytical contexts, such as in harsh chemical environments or when target binding requires unique structural features.

A significant approach involves the use of molecularly imprinted polymers (MIPs) designed to mimic antibody–antigen recognition by polymerizing a monomer mixture around a template molecule (target analyte). After template removal, the polymer retains tailor-made cavities with specific sizes, shapes, and functional-group orientations complementary to the target analyte. This "chemical memory" allows MIPs to rebind the analyte with high affinity and selectivity, making them robust, low-cost alternatives, particularly useful in non-aqueous or extreme conditions where biological molecules might degrade.[36,37]

4. Biosensor devices

The performance of any recognition element is fully realized only when it is integrated into an appropriate device platform capable of transducing molecular interactions into measurable signals. Thus, biosensor devices represent a critical convergence point that combines molecular recognition principles with sophisticated material engineering and signal processing. Over the past few decades, significant advances across microfabrication, nanotechnology, and photonics have driven the development of highly sensitive and miniaturized biosensing platforms essential for detecting small molecules—including critical targets, such as neurotransmitters, hormones, pesticides, and environmental toxins. In this context, the authors have actively contributed to the development of several innovative biosensing systems, including microelectrochemical sensors coupled with microfluidic systems, SPR sensors, electron-multiplying charge-coupled device (EM-CCD)-based fluorescence sensors, and terahertz biosensors, each tailored for sensitive and selective small-molecule detection.

4.1 Electrochemical biosensors

Electrochemical biosensors remain among the most widely used platforms owing to their inherent simplicity, low cost, and scalability. These devices convert molecular binding

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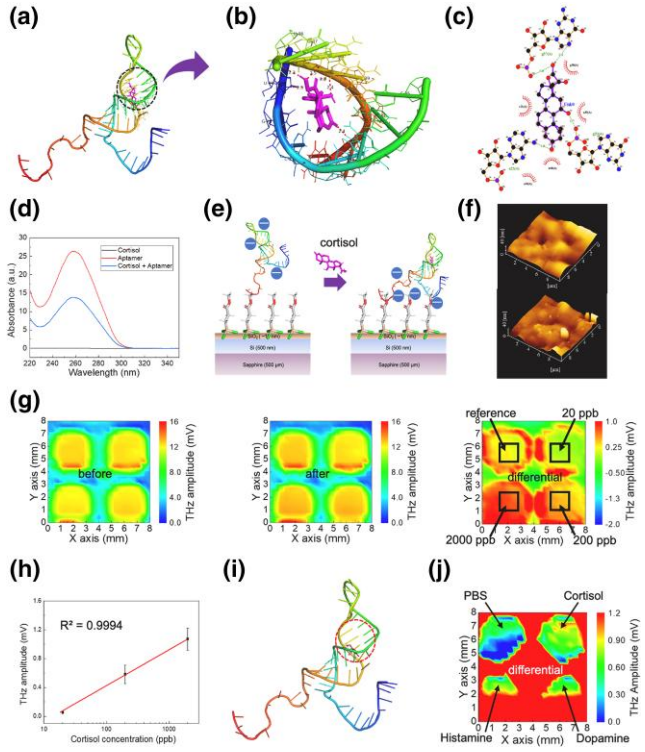

Fig. 5 Validation of the cortisol–aptamer interaction and terahertz sensor performance. (a) and (i) present molecular docking results illustrating the binding of cortisol and histamine/dopamine, respectively, to the DNA aptamer. The binding geometry is further detailed by (b) 3D and (c) 2D illustrations of the cortisol–aptamer complex. (d) Confirmation of the binding event via UV–Vis absorption spectroscopy of the components and the resulting mixture. The operational principle is outlined in (e), showing the measurement concept for the cortisol–aptamer reaction. (f) Surface morphology of the bare and aptamer-modified SiO_2 surface. (g) 2D differential terahertz amplitude maps documenting the spatial distribution of the cortisol–aptamer reaction. (h) Calibration curve for the modified sensor, showing the quantitative relationship between terahertz amplitude change and cortisol concentration ($n = 4$). (j) Sensor's specificity through the differential terahertz mapping of cortisol, histamine, and dopamine at 1 ppm concentration.[31] Copyright (2023) Elsevier.

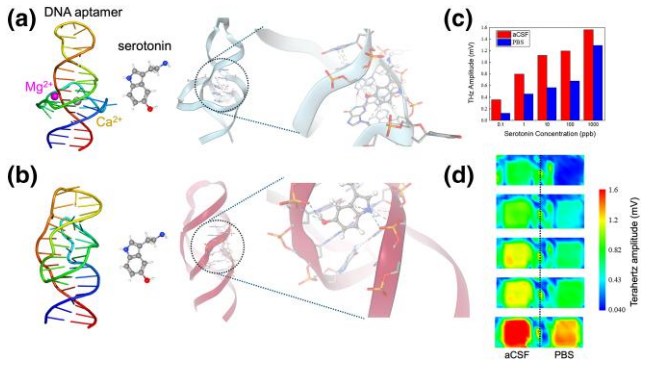

Fig. 6 Alphafold prediction of the DNA aptamer–neurotransmitter complex with magnesium (Mg^{2+}) and calcium (Ca^{2+}) ions (a, b) and terahertz amplitude changes (c, d).[32]

events at the electrode surface into easily measurable electrical signals through amperometry (changes in current), potentiometry (voltage), or impedance spectroscopy.[38–41]

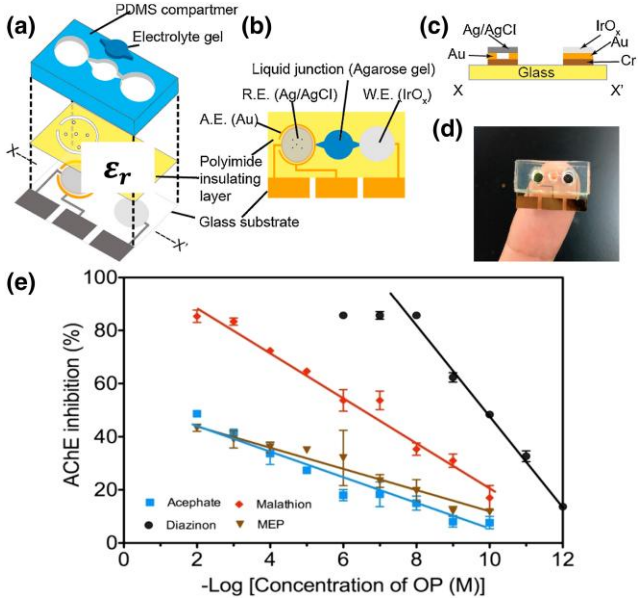

Fig. 7 Construction of a fingertip-sized microelectrochemical sensor coupled with a microfluidic device. (a) Layered construction of the device via an expanded perspective. (b) Planar geometry and the alignment of features across the layers (top view). (c) Vertical arrangement of materials through a cross-section taken at the X–X position. (d) Scale reference of the 20 mm × 11 mm device demonstrated on a finger. (e) Pesticide analysis based on enzyme inhibition.[6,7] Copyright (2014 & 2015) Elsevier.

A wide range of bioinspired recognition elements, including antibodies, enzymes, peptides, and aptamers has been successfully integrated onto electrode interfaces. Figure 7 shows the design and fabrication of a fingertip-sized microelectrochemical sensor coupled with a microfluidic device, showing the layered assembly (Fig. 7a), planar feature alignment (Fig. 7b), and cross-sectional structure (Fig. 7c), as well as the compact device footprint and its application to enzyme-inhibition-based pesticide analysis (Fig. 7d). Nanomaterials such as carbon nanotubes, graphene, and metal nanoparticles, are frequently used to enhance the effective surface area and improve electron transfer kinetics, markedly improving device performance. The development of microelectrochemical arrays and lab-on-a-chip systems has further expanded functionality by enabling multiplexed detection of multiple analytes. These capabilities underpin practical applications in food safety (eg pesticide detection) and rapid clinical diagnostics (eg metabolite quantification).

4.2 Optical biosensors

Optical biosensors, including systems based on SPR, fluorescence, and Raman spectroscopy, offer highly sensitive and label-free detection of molecular interactions. Their versatility is demonstrated across platforms such as peptide-functionalized SPR sensors, DNA aptamer-based fluorescence probes, and plasmonic nanostructure–assisted surface-enhanced Raman scattering devices.[42–44] Although optical biosensors provide real-time monitoring with excellent sensitivity, their dependence on sophisticated instrumentation can limit portability. Figure 8 presents an example of a surface plasmon resonance (SPR) sensor, including the experimental SPR setup and peptide-functionalized gold surface (Fig. 8a), selectivity evaluation toward TNT and its analogues (Fig. 8b). Figure 8d shows

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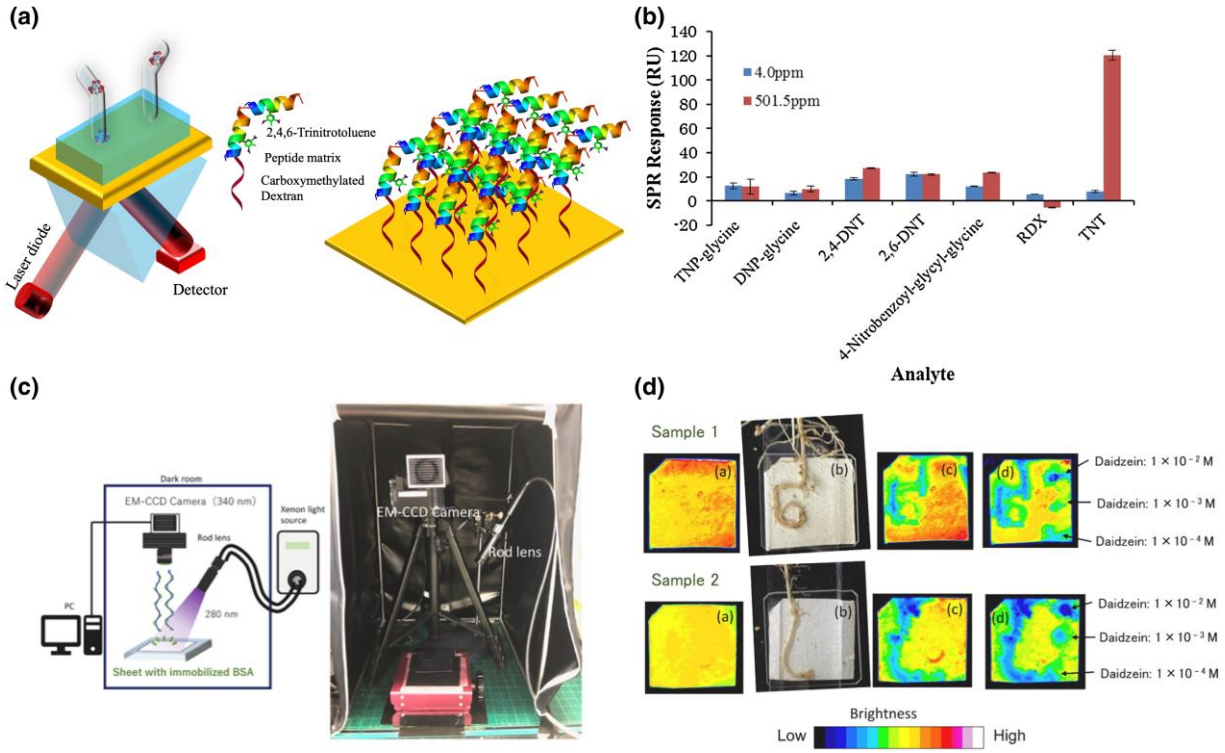

Fig. 8 Example of a SPR sensor. (a) SPR setup and peptide functionalized gold surface, (b) selectivity measurement for TNT molecules and its analogues via an EM-CCD based fluorescence sensor, (c) fluorescence sensor set-up, and (d) rhizosphere daidzein imaging.[5] Copyright (2021) Elsevier.

an EM-CCD-based fluorescence sensor, the corresponding fluorescence measurement configuration, and an application to rhizosphere daidzein imaging.[5]

4.3 Microfluidic and lab-on-chip systems

Microfluidics offers a powerful foundation for miniaturization and integration of biosensor devices into comprehensive lab-on-a-chip systems. These systems enable low-volume sample analysis, multiplexing, and high-throughput screening by precisely controlling fluid flow at the micrometer scale. Successful implementations include enzyme-based pesticide detection chips, peptide-based microarrays, and aptamer-functionalized nanodevices. Combining microfluidics with either electrochemical or optical readouts significantly enhances overall device performance and user-friendliness.

4.4 Versatile terahertz biosensors

TCM is an emerging analytical technique that leverages the extreme sensitivity of terahertz waves to minute changes in surface potential and biomolecular conformations. TCM operates using a unique semiconductor sensing plate, termed SOS, which consists of a thin Si/SiO_2 layer on a sapphire substrate and contains an internal electric field (depletion layer) at the silicon (Si)/silicon dioxide (SiO_2) interface.[45–49] When a high-speed femtosecond laser pulse excites charge carriers in Si, the electric field instantly accelerates them, creating a rapid current change that generates a burst of terahertz radiation. The amplitude of the emitted terahertz wave is directly proportional to the strength of the internal electric field. When a chemical binding event occurs on the surface of the sensor, it slightly shifts the electrical potential, which in turn changes the internal electric field. Therefore, measuring the terahertz wave intensity allows for label-free, real-time mapping of the electrochemical potential distribution with a high spatial resolution determined by the laser focus rather than the terahertz wavelength. By integrating recognition elements—such as DNA aptamers and peptide probes—onto semiconductor substrates, terahertz biosensors enable label-free detection of critical targets, including neurotransmitters, hormones, and hazardous chemicals. Their unique advantage lies in non-destructive, real-time measurement combined with the ability to directly reveal both the charge and conformational dynamics occurring at bio-interfaces. Figure 9 illustrates the TCM system, including the optical architecture of the setup (Fig. 9a), the prototype multifunctional instrument with its terahertz emitter and photoconductive antenna detector (Fig. 9b), terahertz generation on an SOS substrate (Fig. 9c), and representative examples demonstrating its capability for quantitative and real-time neurotransmitter measurements (Fig. 9d–f).

Currently, bio-inspired recognition elements underpin most biosensors and bioelectronic devices designed for small-molecule targets including neurotransmitters, hormones, metabolites, environmental pollutants, and plant secondary metabolites. However, a fundamental limitation persists: the existing repertoire of recognition elements is insufficient to comprehensively cover the immense chemical diversity of small molecules.

This challenge is particularly evident in complex biological samples. For example, a single human breath sample contains more than 1000 VOCs,[50] and reliable disease-specific diagnosis often depends on detecting subtle compositional patterns within this vast mixture. Achieving such specificity would require a large and highly selective library of recognition elements. Given the continuous discovery of novel small

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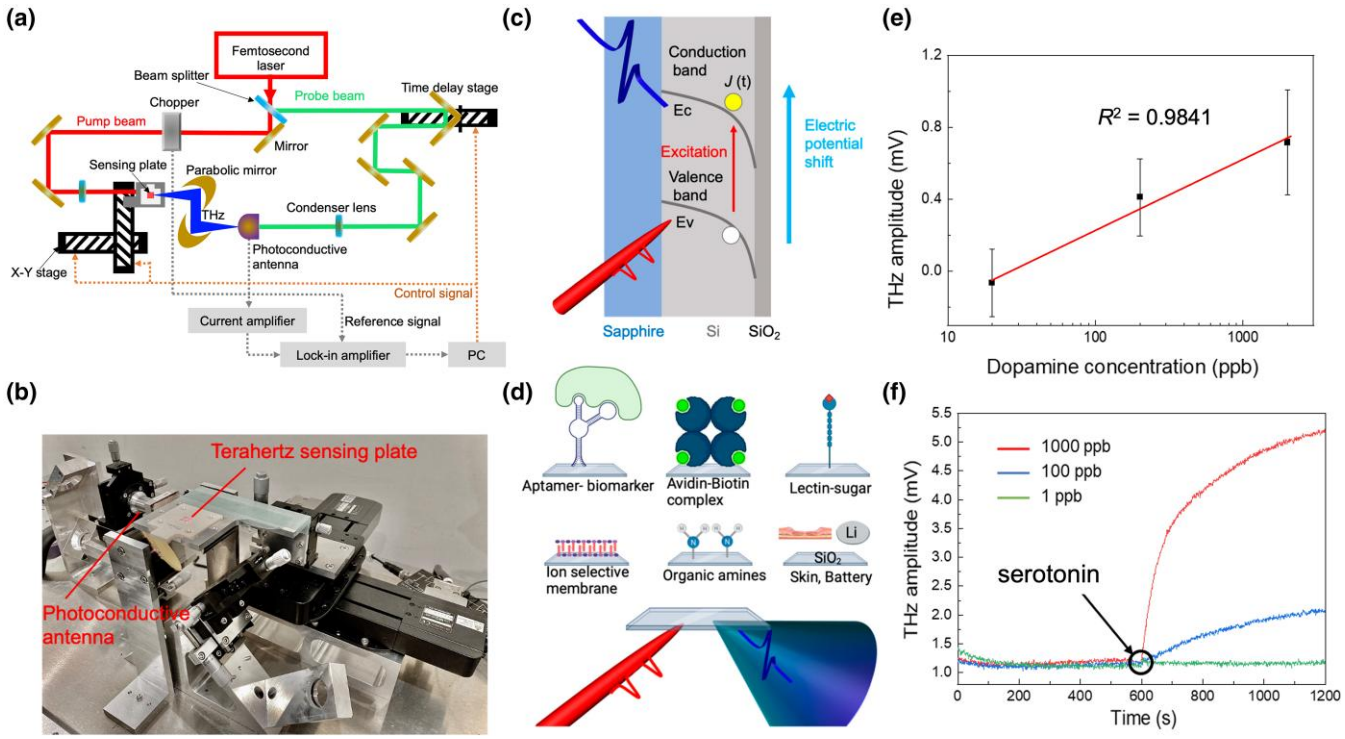

Fig. 9 TCM setup. (a) Schematic of the optical system architecture of the TCM setup.[31] (b) Photograph of the prototype of the multifunctional TCM system, highlighting the terahertz emitter (semiconductor sensing plate) and the photoconductive antenna (terahertz wave detector).[31] (c) Terahertz generation on SOS substrate.[31] (d) A versatile platform enabling quantitative (e) and real-time measurement of neurotransmitters (f). Copyright (2023) Elsevier.

molecules with unique biological functions and physicochemical properties, there is an urgent and unmet demand for next-generation biosensors. These platforms must enable rapid, accurate, and comprehensive measurement of complex small-molecule signatures to advance diagnostics and environmental monitoring.

5. Future directions: emerging AI-guided molecular recognition engineering

Recent advances in AI are poised to reshape the development of molecular recognition elements for small-molecule biosensors.[51–54] While the experimental studies reviewed in this work primarily rely on established bio-inspired strategies—such as antibodies, peptides, and aptamers—the rapid maturation of AI-driven molecular modeling suggests a transformative future pathway for recognition engineering. This section therefore focuses on prospective directions, rather than established achievements, highlighting how AI may complement and extend conventional biosensor design paradigms.

5.1 Conceptual AI workflows for recognition element design

Deep learning and molecular simulations are increasingly integrated to accelerate the discovery of novel molecular recognition elements. Deep learning models—including artificial neural networks (ANNs), graph neural networks, and transformer-based architectures—have shown strong capabilities in predicting molecular interactions and guiding recognition element design. By leveraging structural, sequence, and interaction datasets, such as free-energy profiles or binding affinities (Kd), these models can identify potential binding motifs and estimate affinities with high precision. For example, pretrained protein language models and graph-based encoders now enable virtual screening of peptide and aptamer libraries with significantly greater speed and accuracy than conventional experimental approaches.

These AI-driven methods are further strengthened by large-scale molecular dynamics (MD) simulations and free-energy (ΔG) calculations, which provide essential mechanistic validation. AI tools can accelerate force field parameterization, predict folding pathways, and rapidly estimate binding affinities, thereby refining candidate selection. MD simulations also reveal conformational changes upon small-molecule binding, offering mechanistic insights that purely data-driven models may overlook. When coupled with high-throughput in silico screening, this integrated approach greatly reduces experimental costs and effort, enabling identification of the most promising recognition elements before synthesis and laboratory validation. Figure 10a illustrates conceptual AI-enabled modeling pipelines for future binder design. The workflow initiates with RFdiffusion for generative backbone synthesis,[55] followed by amino acid sequence assignment using dedicated sequence-design models such as ProteinMPNN.[25,56] The resulting candidates then undergo refolding and structural validation using AlphaFold or Boltz-2, which provide RMSD-based evaluation and confidence scoring.[20] Backbone structures are initially generated using BoltzGen, while Boltz-2 further enables ligand-aware structural assessment relevant to small-molecule binding.[16,57] Figure 10b illustrates the workflow proposed in this study for peptide and DNA aptamer design, integrating MD simulations, Rosetta-based modeling, and ANN-based screening to guide small-molecule specificity.

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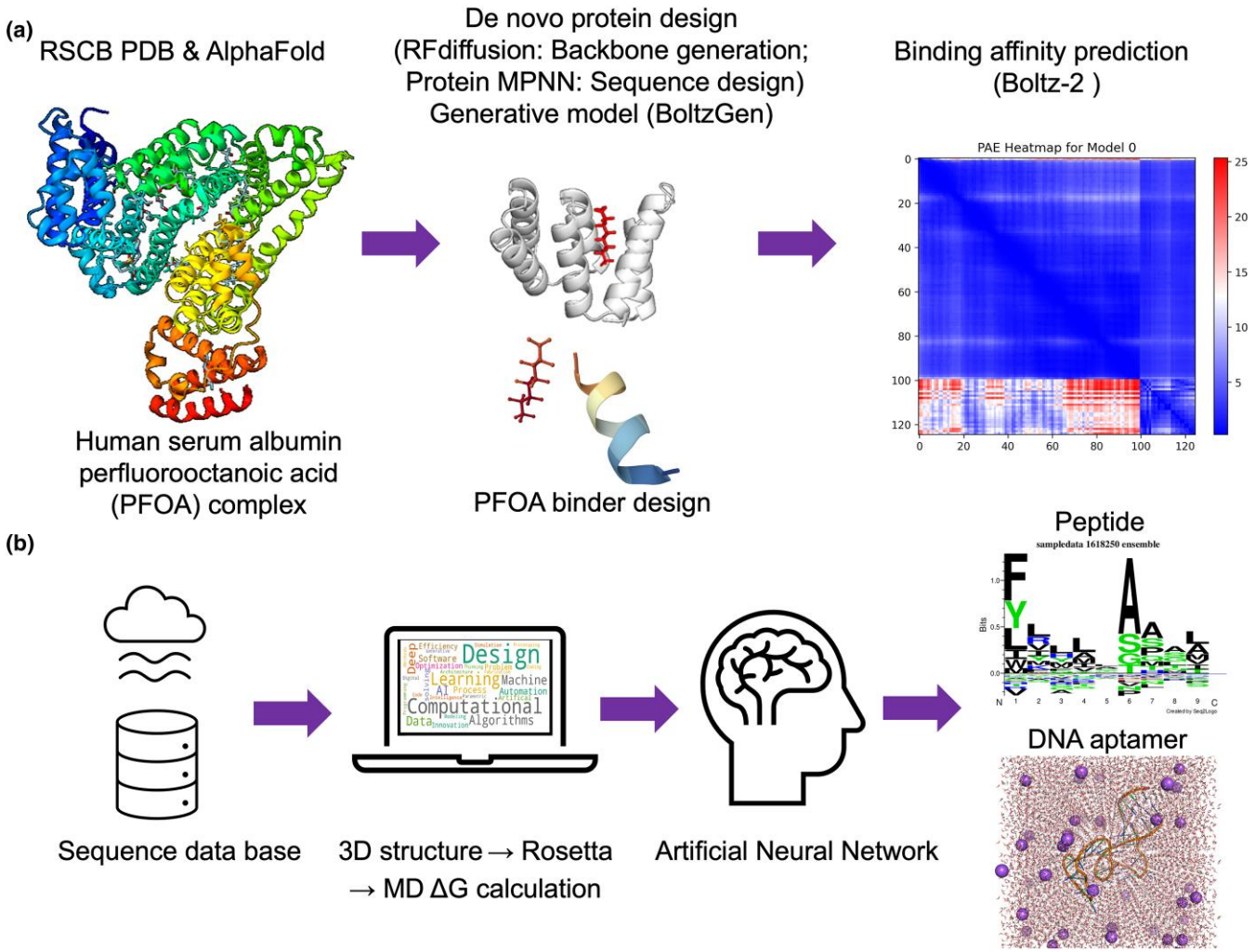

Fig. 10 AI-guided molecular recognition engineering workflows. (a) Conceptual pipeline for de novo design of a PFOAbinding protein. (b) Workflow proposed in this study for peptide and DNA aptamer design using MD, Rosetta, and ANN screening.

5.2 Challenges and outlook

Despite these advantages, significant challenges remain for the development of AI-driven molecular recognition. Limitations in data availability, interpretability, and generalizability continue to constrain progress. Comprehensive and high-quality training datasets capturing small-molecule–biomolecule interactions remain scarce, and the ability to transfer models across chemical and biological domains remains underdeveloped. Furthermore, the lack of transparency in AI predictions raises concerns regarding biomedical applications, where explainability is crucial for ensuring trust and adoption.

Future directions are likely to focus on self-supervised and foundational learning approaches, integration of multi-omics datasets, and co-design strategies that optimize recognition elements alongside biosensor device architectures. Such approaches aim to overcome current bottlenecks by creating models that are both data efficient and biologically interpretable. Ultimately, the long-term vision is the establishment of autonomous discovery platforms in which AI continuously designs, evaluates, and evolves recognition elements. Such a paradigm could transform biosensing into a self-adaptive technology and accelerate the emergence of next-generation biosensor systems.

6. Conclusion

The pursuit of precise small-molecule detection, from neurotransmitters and hormones to environmental toxins, is being fundamentally reshaped by the convergence of AI and advanced materials science. As outlined in this Account, the author has systematically navigated the evolution of small-molecule biosensors, demonstrating a clear trajectory from traditional bio-inspired strategies toward a predictive, AI-guided discovery framework.

The contributions span the full biosensor spectrum, starting with foundational molecular recognition engineering, including the successful development of peptide recognition elements derived from monoclonal antibodies and the integration of diverse binders (peptides, aptamers, and enzymes) into practical platforms. Significant advancements in device miniaturization and signal transduction are demonstrated through enzyme-based microelectrochemical arrays for multiplex pesticide detection, high-performance peptide-based surface plasmonic sensors, and innovative DNA-aptamer-based terahertz sensors for label-free real-time monitoring. Collectively, these studies illustrate how advances in microfluidics, nanotechnology, and specialized optical and electrical readouts maximize the utility of engineered recognition elements.

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Most recent work underscores a critical shift toward AI-guided design. By leveraging deep learning, generative algorithms such as RFDiffusion and Rosetta, and high-throughput simulations, it is now possible to perform rational de novo design of molecular probes (proteins, peptides, and aptamers) with markedly improved selectivity, affinity, and stability. These approaches directly address longstanding limitations such as data scarcity and chemical space coverage. Although challenges related to data availability and model interpretability remain, future directions point toward autonomous discovery platforms and co-optimization of recognition elements with sensor architecture. Ultimately, the integration of AI with device engineering holds the potential to establish biosensing as a self-adaptive technology, accelerating the emergence of next-generation sensor systems capable of rapid, accurate, and comprehensive small-molecule detection across diagnostic and environmental applications.

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Data availability

This manuscript was prepared with the support of an Award Account. Because no experimental work was conducted, no data are available for disclosure.

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