Chemical Science

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2025, **16**, 20139

Intelligent molecular logic computing toolkits: nucleic acid-based construction, functionality, and enhanced biosensing applications

Yaxue Hu, [a] Jinghui Zhang, *[a] Ke Shen,[a] Wei Shen, [a] Hian Kee Lee *[ab] and Sheng Tang *[a]

Molecular logic computing is revolutionizing biosensing by enabling intelligent, programmable detection, moving beyond simple target recognition to advanced molecular-level information processing. By employing biological molecules such as DNA/RNA, proteins/enzymes, or even whole biological cells as building blocks for creating molecular logic toolkits, logic operations have made rapid progress in molecular logic-based biosensing. In this review, we present a comprehensive overview of intelligent molecular logic operation toolkits and their contributions to advancing biosensing technologies. We first outline the design principles of these toolkits, detailing various types of logic gates, including Boolean, combinatorial, and sequential logic, as well as advanced feedback systems, fuzzy logic, and reversible logic. We delve into the construction of DNA-based, synthetic, and nanomaterial-based logical operation toolkits. Following this, we explore the functionalities of intelligent molecular logic computing toolkits, which encompass modular multi-signal integration, activatable lock–key (OFF–ON) reconfigurable control, programmable control, and logic-gated nanomachines. We also elaborate on the analytical mechanisms underpinning molecular logic-gated operations that utilize various detection platforms, including fluorescent, colorimetric, and electrochemical techniques, along with artificial intelligence-powered and smartphone-based detection platforms. Applications spanning genetic analysis, cancer analysis, pathogen identification, living cell logic analysis, and point-of-care diagnostics are highlighted. Finally, the future challenges associated with molecular logic toolkits in enhancing biosensing and potential solutions were outlined, providing insights into practical obstacles as well as future trends and prospects.

Received 13th August 2025
Accepted 16th October 2025

DOI: 10.1039/d5sc06176h

rsc.li/chemical-science

[a]*School of Environmental and Chemical Engineering, Jiangsu University of Science and Technology, Zhenjiang 212003, Jiangsu, PR China. E-mail: jinghui_zhang@just.edu.cn; tangsheng.nju@gmail.com; chmts@just.edu.cn*

[b]*Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Singapore. E-mail: chmleehk@nus.edu.sg; hiankeelee@u.nus.edu*

Yaxue Hu

Yaxue Hu is a graduate student in the School of Environmental and Chemical Engineering at Jiangsu University of Science and Technology, Zhenjiang, China. Her research focuses on the development and application of DNA-based logic devices for bioanalytical sensing, with particular interest in biosensing platforms and molecular diagnostics.

Jinghui Zhang

Jinghui Zhang is an associate professor in the School of Environmental and Chemical Engineering at Jiangsu University of Science and Technology. She received her PhD in Chemistry from Hunan University, China, in 2021. Her research focuses on developing innovative approaches for nucleic acid analysis, designing DNA-based logic devices, and engineering nanomaterial-based biosensors for diagnostic applications.

1 Introduction

Today, silicon-based computing systems are widely used in various aspects of our lives due to their powerful computing capabilities and remarkable implementation. These silicon-based computing systems operate using intelligent electronic circuits known as logic gates, which can make logic decisions based on input parameters to produce discrete outputs.[1–3] Unlike analog circuits, which can provide a continuous range of values, logic gates only offer two discrete binary outputs, 0 and 1, representing false and true.[4] This type of operation disregards the chaotic signal between 0 and 1, focusing only on determining true or false. This simplifies computer calculations and enhances communication between humans and machines, making logic operations widely used in silicon-based computer systems.[1] However, as semiconductor sizes continue to shrink, the Moore limit hinders the further development of silicon-based operations.[5,6] Additionally, silicon-based circuits cannot function in bio-electrolyte solutions, making it impossible to study the molecular parameters of living organisms, especially in biosensing.

Currently, researchers are exploring alternative solutions to improve computing power in various application scenarios. In this pursuit, novel intelligent molecular logic computing, as a molecular-level functional simulation of silicon logic equivalents, has captured significant attention and offered a unique vision for enabling diverse intelligent applications.[4,7,8] Molecular logic computing represents a fundamentally distinct paradigm from traditional silicon-based electronics in information processing. While this approach encounters certain challenges, including limited operational speed due to chemical kinetics, difficulties in cascading gates and achieving fan-out, restricted programmability, and concerns about stability (as outlined in Table 1), its unique advantages are considerable. First, as comprising small molecular clusters, molecular logic gates offer a theoretical integration density that surpasses the physical limitations of silicon-based chips, potentially alleviating the scaling and economic constraints associated with

Ke Shen

Ke Shen is a graduate student at the School of Environmental and Chemical Engineering, Jiangsu University of Science and Technology. His research focuses on biochemical analysis and the development of nanomaterial-based biosensors for advanced diagnostic applications.

Hian Kee Lee

Hian Kee Lee is a professor at the Department of Chemistry, National University of Singapore, and is a Fellow of the Royal Society of Chemistry, the Singapore National Academy of Science and the Academy of Sciences Malaysia. He received his BSc (Honours) and PhD degrees from the University of Canterbury, New Zealand. Since 2022, he has also been a "Distinguished Academician" at Jiangsu University of Science and Technology. Professor Lee has an interest in environmental analytical chemistry, specifically with reference to the development of miniaturized sample preparation procedures.

Wei Shen

Wei Shen is a professor in the School of Environmental and Chemical Engineering at Jiangsu University of Science and Technology. She received her BSc degree in Chemistry from Zhejiang University, China (2011) and PhD degree in analytical chemistry from the National University in Singapore (2016). Her research interests focus on the development of advanced materials for bioanalytical applications.

Sheng Tang

Sheng Tang is a professor in the School of Environmental and Chemical Engineering, Jiangsu University of Science and Technology. He received his BSc degree in chemistry from Nanjing University, China in 2011 and his PhD degree in analytical chemistry from the National University of Singapore in 2016. His research interests include the synthesis and application of novel nanomaterials for biosensors and the design of innovative extraction processes. He has been an editor of the International Journal of Analytical Chemistry and the Chinese Chemical Letters since 2022.

Table 1 Comparison: molecular logic computing *vs.* silicon-based electronic logic computing

Dimension of comparison	Molecular logic computation	Silicon-based electronic logic computation
Relative advantages	**Biocompatibility**: operate in aqueous/biological environments, enabling direct integration with biochemical systems	**High operational speed**: extremely fast processing speed
	Functional diversity: diverse molecular structures allow for customized functionality	**High technological maturity**: possesses a highly mature manufacturing and global ecosystem
	Ultra-low power consumption: energy use per molecular switch is extremely low, approaching the theoretical limit	**High reliability & stability**: stable performance with low error rates, meeting industrial standards
Key limitations	**Slow speed**: switching and response times are very slow	**Physical scaling limit**: micro/nano-fabrication is approaching the physical miniaturization limit of silicon transistors
	Signal interfacing challenge: molecular signals are difficult to transmit over long distances and have weak driving capability	**High power consumption & heat dissipation**: high integration density leads to significant power consumption
	Limited functionality & programmability: function is often determined by chemical structure, lacking general programmability	**Rigid structure & application limits**: devices are rigid and difficult to apply directly in flexible electronics or within living organisms
	Environmental instability: relatively poor stability, susceptible to interference from the chemical environment	**von Neumann bottleneck**: the von Neumann bottleneck constrains overall data processing efficiency
Critical challenges	**System integration & scaling**: overcoming cascading and fan-out challenges to integrate molecular devices into complex circuits	**Extending Moore's law**: exploring new materials and architectures to break performance bottlenecks
	Input/output standardization: establishing reliable methods for signal input, output, and readout to solve the signal conversion problem	**Power & thermal management**: optimizing designs from materials to systems to address high power density and heat dissipation issues
	Transition to practical systems: advancing the technology from laboratory proof-of-concept to practical systems	**Reliability & security**: addressing new failure mechanisms from process scaling to ensure chip security and reliability

photolithography.[7] Additionally, rather than relying solely on electrons, molecular logic employs a variety of information carriers, such as ions, photons, and redox species, for inputs and outputs. This often results in significantly lower energy consumption compared to electron movement in semiconductor circuits. Lastly, a critical advantage of molecular logic is its biocompatibility. Many molecular logic gates function optimally in aqueous environments, including physiological buffers and within living cells – conditions that typically hinder silicon-based devices. This intrinsic compatibility offers a remarkable capability for direct bio-interfacing, facilitating seamless integration with biological systems.[9]

Molecular logic computing involves using a molecular substrate as a computing device to process physical or chemical inputs and produce outputs using logic operators.[9,10] Since de Silva developed the first molecular logic gate,[11] scientists have focused on using molecular simulations of the fundamental components of integrated circuits to enable intelligent computing. It is now ready for diverse practical applications, venturing into new areas untouched by silicon-based logic gates. Scientists can create synthetic molecular systems and nanoscale supramolecular materials by simulating Boolean logic gates.[7] These cutting-edge systems demonstrated basic arithmetic and memory functions by integrating light, chemistry, or electrochemistry technologies, making molecular logic computing ready for many potential practical applications. In molecular logic computing, molecules can respond to changes in biological microenvironments, such as ions, biological substances, pH, viscosity, temperature, and pressure.[9,12] As a result, these molecules can function as binary-coded inputs (present 1, non-existent as 0) and produce optical (colorimetric, fluorescent, luminescent) or electrochemical signals as outputs. Therefore, molecular logic gates are widely used in the biosensing field. They have become versatile toolkits for multi-scenario biosensing, greatly promoting sensing analysis, timeliness, intelligence, and accuracy.

In the field of molecular logic biosensing, biomolecules such as proteins and deoxyribonucleic acid (DNA) have been used as building blocks to create molecular logic-based sensors. By employing biomolecules like DNA/RNA, proteins/enzymes, and even entire biological cells, in combination with concepts from systems biology, significant advancements have been achieved in the development of molecular logic sensors.[13–15] One of the advantages of biomolecular logic computing systems is their ability to be integrated into complex artificially designed chemical processes to simulate multi-step information processing networks.[16,17] These molecular logic computing sensors are capable of monitoring cellular components as inputs and generating outputs that are relevant to medical diagnosis and treatment.[12,18] The sensors can operate by reading fluorescence, colorimetric, or electrochemical signals that are linked to the output port and indicate the presence (1) or absence (0) of a specific compound.[19,20] Thus, there are high expectations for

expanding molecular logic computing toolkits into biochemical sensing systems.

Nucleic acid-based sensing, as a significant sensing direction in the biosensing field, plays a vital role in clinical diagnosis, genotyping and therapy. This field has gained increased importance with the Human Genome Project[21–23] and the current novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2).[24–26] Nucleic acids possess unique Watson–Crick base complementary pairing properties, allowing for precise information transduction between nucleic acid chains and base pairs, which coincides with the development needs of molecular logic toolkits.[27,28] Nucleic acids can serve as targets or components of logic gates for molecular logic-based biosensing due to their biocompatibility and programmable properties. Consequently, research into nucleic acid-based sensing and detection strategies, including nucleic acid target detection and its application as a sensing tool, holds significant value in bioanalytical chemistry.[29,30] In recent years, nucleic acid-based biosensors have been designed and applied to enable biomedical functions such as targeting, imaging, sensing and therapy.[31–34]

However, the traditional nucleic acid sensing has long operated under a "one target, one output" linear model. While this approach can be effective in simpler scenarios, it faces significant challenges in complex biological systems, such as the inability to interpret intricate molecular states and logical relationships, weak anti-interference capability, and limited information output dimensions. As a result, it falls short of meeting the growing demands for analytical complexity, high specificity, and intelligent data processing. In contrast, molecular logic-gated sensing presents a more reliable alternative and integrating signal processing capabilities. This molecular logic possesses a natural ability to interpret complex biological logics, demonstrates intrinsic resistance to environmental noise, and supports multiplexed intelligent outputs.[12,35] Together, these attributes transform these sensors from mere passive signal transducers into active information processors. Furthermore, these biosensors have been combined with logic-gated functions to facilitate rapid molecular logic operations, underscoring the growing impact of this field in chemistry. This evolution represents a significant technological advancement, propelling *in vitro* diagnostics towards unparalleled precision and paving the way for a new era in intelligent biosensing and theranostics.

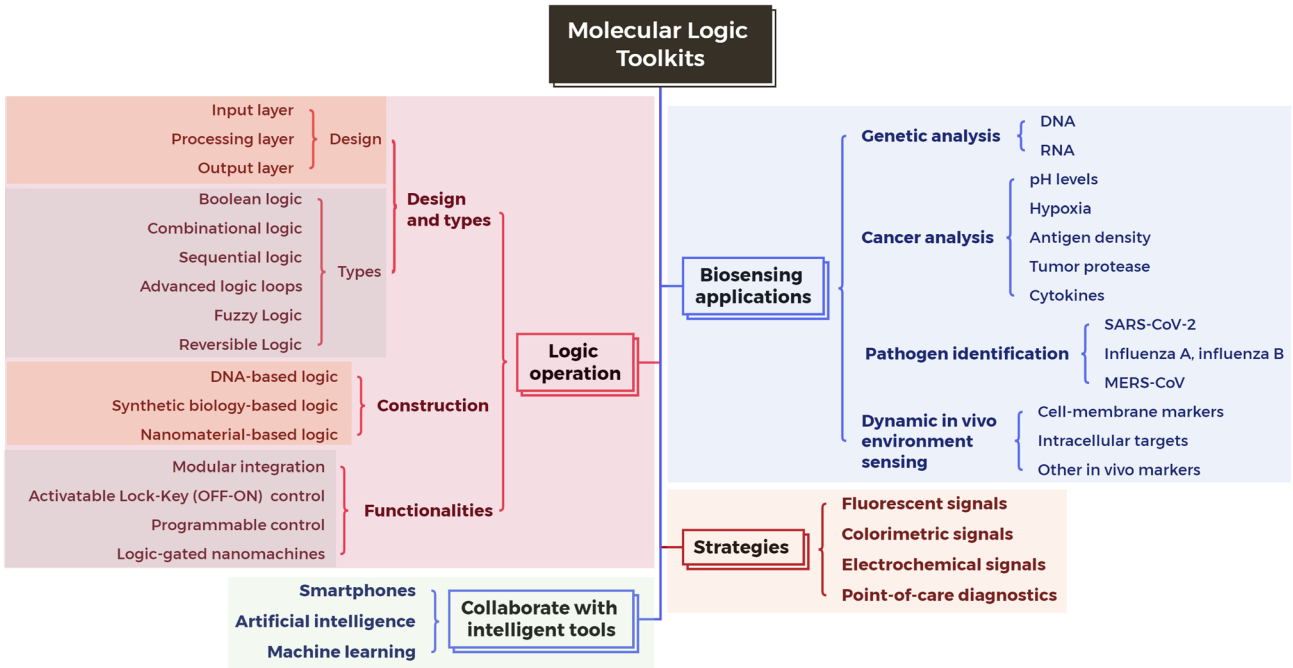
In recent years, nucleic acid-related biosensing based on molecular logic operation has been a hot research topic, and numerous studies have been conducted. Several reviews have also been published on this topic. For instance, Bose *et al.* reviewed logic devices for biomolecular computing;[12] Fan *et al.* reported on advancements in innovative DNA logic computing nanostructures and smart bio-applications;[36] and Yin *et al.* summarized biosensors based on DNA logic gates, focusing on the biosensors in solution, at interfaces, and in cellular environments.[34] While existing reviews have explored logic computing in bio-applications (such as cell-related biosensing and smart logical diagnostic devices), a systematic new evaluation of their role in enhancing biosensing is still required. This gap is particularly evident in the lack of comparative analysis covering the design, construction strategies, and functionalities of diverse logic paradigms from Boolean and combinatorial to sequential logic, advanced feedback systems, fuzzy logic, and reversible logic. To fill this significant gap, the present article provides the first systematic review focusing specifically on biosensing advancements driven by intelligent molecular logic computing toolkits. In this review, not only DNA-based logic computation, including DNAzyme-based and enzyme-free DNA logic computation, but also synthetic and nanomaterial-based logic computation toolkits are introduced. The key functionalities, such as modular multi-signal integration, activatable lock–key (OFF–ON) control, and programmable logic-gated nanomachines, are explored. Furthermore, the applications in genetic analysis, cancer diagnostics, pathogen identification, point-of-care testing, and dynamic *in vivo* environments are surveyed (Scheme 1), highlighting their roles in the enhancement of biosensing. In addition, the underlying analytical mechanisms, including optical, electrochemical, and intelligent sensing approaches integrated with smartphones and artificial intelligence (AI), are elaborated. Finally, the current challenges in translating these toolkits from proof-of-concept to practical application, potential solutions, and the future developmental trends are conjectured, aiming to provide a fresh and critical perspective on the evolving field of molecular logic-gated computing.

2 Design and construction of intelligent molecular logic computation

2.1 Design of nucleic acid-based molecular logic computation

2.1.1 Design principles and concepts. Molecular logic represents a novel paradigm for information processing, which utilizes molecules, rather than silicon-based electronics, as fundamental computing units. By embedding information-processing capabilities directly into matter, it enables intelligent recognition, decision-making, and response within complex chemical or biological environments such as living systems, medical diagnostics, and environmental monitoring.[37,38] As illustrated in Fig. 1, molecular logic systems are typically designed into three functional layers: the input layer, the logic processing layer, and the output layer.

The input layer functions as the interface for detecting external chemical or physical signals, which serve as the initial conditions that trigger logical operations. Common input modalities in the design of this layer include biological inputs (*e.g.*, DNA, enzymes, antibodies, or pathogens), chemical inputs (such as specific ions or small molecules), and physical inputs (including light, temperature, or electric fields). Unlike traditional computers, which rely on electrical signals, molecular logic systems operate through direct interaction with environmental variables. This allows seamless integration into biological or chemical milieus without the need for complex signal transducers or external sensors.



Scheme 1 Flowchart of intelligent molecular logic computing toolkits for nucleic acid-based biosensing.

The logic processing layer acts as the "brain" of the molecular logic system. It receives signals from the input layer and performs computations according to predefined Boolean logic operations, such as AND, OR, XOR, and INHIBIT. The molecular-level design of this layer can be achieved through various strategies, including DNA-based computing, synthetic biology-driven logic, and nanomaterial-mediated logic operations. In DNA-based molecular logic computing, input signals, such as specific DNA sequences, ions, or small molecules are interpreted as binary inputs (0 or 1). The computation proceeds through molecular interactions like DNA hybridization, strand displacement, or enzyme-driven reactions, resulting in a detectable output signal.[39,40] Synthetic biology-based logic employs genetic engineering to build biomolecular logic gates from DNA, RNA, or proteins. These circuits control gene expression in response to logical operations (*e.g.*, AND, OR,

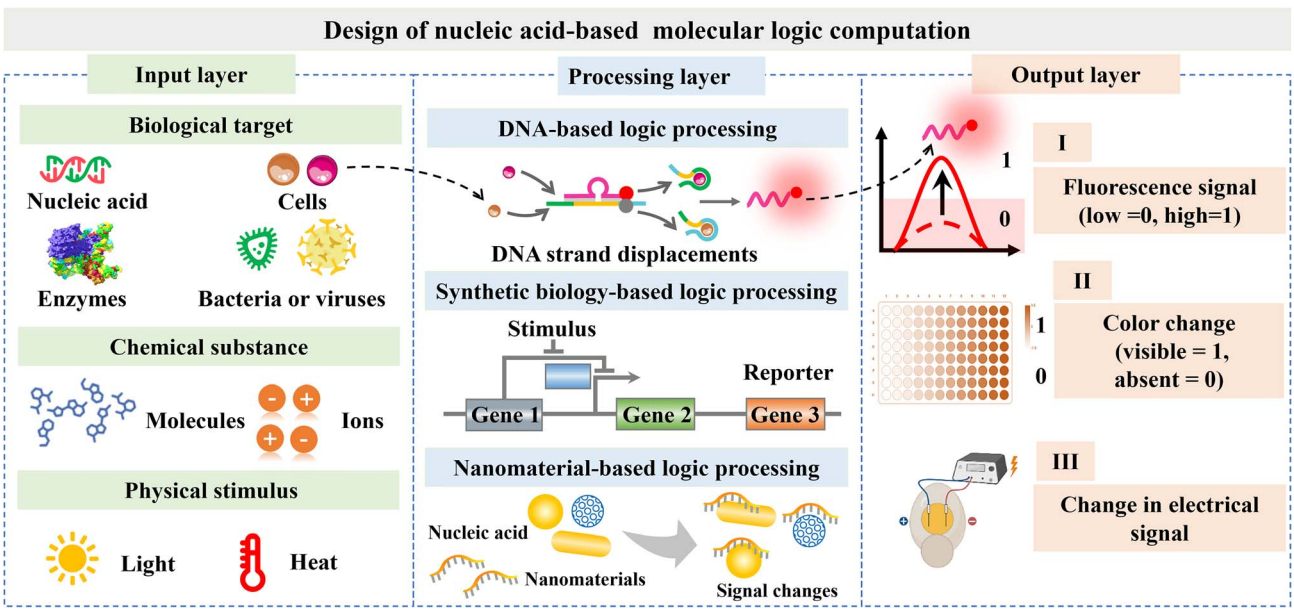


Fig. 1 Design principles of nucleic acid-based molecular logic systems through three functional layers: input layer, logic processing layer, and output layer.

NOT), thereby enabling programmable cellular functions.[41,42] Nanomaterial-based logic employs materials like metal nanoparticles, carbon nanotubes (CNTs), or quantum dots as both the fundamental computing elements and signal transducers. Interactions with nucleic acids or other input stimuli induce quantifiable alterations in the physical properties of these nanomaterials, resulting in a measurable response that encodes the output of the logic operation.[43,44]

The output layer serves as the interface through which a molecular logic system communicates the results of its computations. It converts the outcomes processed by the logic layer into readable and actionable signals. Common output modalities include optical signals such as changes in fluorescence intensity or color, as well as electrochemical signals and other measurable physical or chemical changes. Meanwhile, the output often constitutes a direct action rather than mere data. For example, the system may be designed to recognize and kill targeted cells, trigger an immune response, or release therapeutic agents.[45,46]

From a three-layer architectural perspective, molecular logic represents a shift in information processing. It relocates "intelligence" from macroscopic computer chips and embeds it directly into molecules. This seamless integration of computation and execution enables the system to autonomously complete a "sense-compute-act" cycle without human intervention, facilitating direct molecular-level decision-making and operation. This approach empowers matter itself with the ability to perceive, compute, and act, advancing the convergence of chemistry, materials science, biology, and information science.

2.1.2 Different types of logical computing. At present, the primary types of logic operations encompass Boolean logic, combinatorial logic, sequential logic, advanced logic loops and feedback systems, fuzzy logic, and reversible logic. As illustrated in Table 2, these logic paradigms are systematically compared based on their theoretical foundations, input/output behavior, key characteristics, and typical applications.

Boolean logic is the most fundamental logic circuitry, based on George Boole's algebraic system. It operates using binary variables that can assume only two values: TRUE (1) or FALSE (0). Key operations such as AND, OR, and NOT are defined through truth tables. In Boolean logic, the inputs and outputs are distinctly binary, meaning that one or more binary inputs produce a single binary output based on the specified logical operation. Its main characteristics include simplicity, determinism, and a binary structure. The output is determined exclusively by the current combination of inputs, without any memory capability. Applications of Boolean logic are diverse, ranging from molecular computation using DNA to create artificial chemical reaction networks (CRNs) that execute Boolean logic tasks,[47–49] to gene editing techniques that utilize Boolean logic for spatiotemporally regulated genome editing and intelligent delivery systems.[50]

Combinational logic refers to circuits composed of Boolean logic gates, where the output is determined solely by the current combination of inputs and does not depend on prior inputs or internal states. These circuits operate according to the principles of Boolean algebra. The inputs consist of various combinations of binary signals, and the output is a direct function of the current input values. Key characteristics include the absence of memory (the output is independent of input history), the lack of feedback loops, and the presence of propagation delay, which serves as a significant limiting factor. Typical applications encompass arithmetic logic units, encoders and decoders, multiplexers and demultiplexers, and parity checkers. Additionally, combinatorial logic supports advanced applications such as translating upstream pathway information into binary DNA codes for downstream DNA-based circuits and nucleic acid computing,[51] as well as enabling the design of sophisticated multiplexing systems.[52,53]

Sequential logic refers to a type of logic circuit where the output is determined not only by the current input but also by the sequence of previous inputs, which is known as the present state. This type of logic is typically modeled using finite state

Table 2 Different types of logical computing

Logic type	Theoretical basis	Input; output	Key features	Typical applications
Boolean logic	Boolean algebra, binary system	Single/multiple binary inputs; single binary output	Binary values (0/1), deterministic, memoryless	Basic digital gates, simple decision circuits
Combinational logic	Boolean algebra, combinatorial Boolean logic circuit	Combination of binary inputs; binary output	Output depends only on current inputs, memoryless, no feedback	Adders, multiplexers, encoders/decoders
Sequential logic	Finite-state machine, sequential circuit theory	Current input + clock + current state; output + next state	Memory elements, output depends on input history and state, uses feedback	Counters, shift registers, memory units
Advanced logic loops	Cybernetics, dynamical systems theory	External input + feedback input; system output	Feedback loops, dynamic, non-linear, oscillatory	Oscillators, bistable switches, adaptive systems
Fuzzy logic	Fuzzy set theory, approximate reasoning	Crisp values (fuzzified); fuzzy values [0,1] (defuzzified)	Handles partial truth & uncertainty, rule-based	Intelligent control, encoding, encryption, and concealment systems
Reversible logic	Thermodynamics, quantum mechanics	Equal number of inputs and outputs (one-to-one mapping)	Information conservation, low power consumption, foundational for quantum computing	Ultra-low-power circuits, quantum algorithms, nano-computing

machines. Inputs to sequential logic comprise both data inputs and a clock signal, with the output being a function of the combination of current inputs and the current state. Key characteristics of sequential logic include memory capabilities, enabled by storage elements such as flip-flops and latches, the presence of feedback loops, and reliance on clock signals for synchronization in synchronous sequential logic. Common applications include counters, shift registers, memory units, microprocessor control units, and state management in digital systems.[54–56] Sequential logic circuits based on DNA strand displacement can be utilized to model signal processing events in biological systems that involve time-dependent information.

Advanced logic loops and feedback systems are based on the principle of reintegrating a system's output as input (feedback), which results in dynamic and often nonlinear behaviors. This concept is rooted in cybernetics and dynamical systems theory. Inputs to these systems typically encompass both external stimuli and feedback signals; the output is determined by the current state of the system and the inputs received, which are then looped back into the system. These systems are characterized by feedback loops and the ability to exhibit complex dynamic behaviors like oscillation, bistability, and chaos. Furthermore, they can support memory and adaptive functions.[57–59] In 2011, Winfree *et al.* developed a synthetic oscillator utilizing transcriptional regulatory components, including promoters, repressors, and feedback loops.[58] The DNA-based oscillators offered new functionalities for DNA computing, including the generation of precise timing signals to synchronize different operations and recognize specific patterns. These advances demonstrated that DNA-based networks were capable of supporting more sophisticated functions, such as dynamic and continuous signal processing.

Fuzzy logic expands upon Boolean logic by incorporating the concept of "partial truth", where truth values can range continuously from 0 (completely false) to 1 (completely true), rather than being limited to just 0 or 1. It is grounded in fuzzy set theory. Inputs can be either precise or fuzzy values, which are transformed into degrees of membership through a process known as fuzzification. Outputs are represented as fuzzy sets, which are often converted into precise values *via* defuzzification. Key characteristics of fuzzy logic include its capability to manage uncertainty and approximate reasoning, the use of linguistic variables, and rule bases (such as IF-THEN rules), all of which allow it to emulate human decision-making processes effectively. Fuzzy logic enables a broad range of applications within electrochemical molecular systems, including sensing, logic computation, encoding, encryption, and steganography.[60,61] For instance, Huang *et al.* have devised a novel perception method grounded in fuzzy logic that employed acridine orange dye-graphene as a nano-filter and nano-switch. This approach capitalized on graphene's capacity to interact with DNA structures of varying conformations.[62] The system mimicked human reasoning to tackle complex nonlinear challenges, transforming numerical outputs into linguistic descriptions applicable in biochemical systems, environmental monitoring, and molecular-level fuzzy logic computing. The authors also successfully developed a graphene-based chemical system that could implement Boolean logic trees. This system supported both fluorescent combinational logic, including basic gates and complex integrated circuits, as well as fuzzy logic computations.[63] This facilitates the development of advanced molecular-based logic programs for applications in biosensing, nanotechnology, and drug delivery. Furthermore, they developed a graphene-based steganographic aptasensing system that functioned as a dual cryptographic and steganographic platform for information computation, encryption, hiding, fluorescence sensing, and *in vivo* imaging of fish pathogens.[64] By enhancing material composition and system functionalities, this platform could be expanded to facilitate multimodal colorimetric sensing, advanced logic computing, and multi-layer information protection with improved anti-interference capabilities.[65] It allowed for the encoding, encryption, and concealment of specific information, such as notable quotations and literary excerpts, thereby advancing the fields of nano-cryptography and steganography.

Reversible logic is rooted in principles from thermodynamics and quantum mechanics. It encompasses a category of logic operations where information is preserved, allowing for the unique reconstruction of the input vector from the output vector without erasing any information during computation, in line with Landauer's principle.[66] The fundamental requirement for reversible logic is that the number of input lines must match the number of output lines, ensuring a one-to-one mapping that prevents information loss. Key characteristics of reversible logic include its significance in ultra-low-power design, its foundational role in quantum computing, and the reversibility of its logic gates. For example, Li *et al.* demonstrated a reversible logic circuit created through the programmable assembly of interlocked nanostructures based on double-stranded DNA (dsDNA) pseudorotaxanes, which facilitates the repetitive operation of a DNA-based computing unit.[67] A significant challenge in improving the computational capabilities of nucleic acid-based molecular logic is the issue of reusability. To tackle this problem, Liu *et al.* introduced a highly reusable enzyme-driven DNA logic circuit that utilized the selective cleavage activity of Exonuclease III to reset the reaction system from its final state back to the initial state.[40] This reset mechanism enabled the logic circuit to be executed multiple times. The reuse strategy demonstrated exceptional performance in both single-gate and multi-level cascade systems with varying input conditions.

2.2 Construction of nucleic acid-based molecular logic computation

2.2.1 DNA-based logic computation. DNA, was originally considered as a carrier of genetic information based on the principle of base complementarity. Due to its distinctive properties, such as binding specificity and structural stability, it plays a crucial role in the design of molecular machines and sensing components, facilitating molecular recognition and information processing.[68,69] The construction of a nucleic acid-based intelligent logic computing system relies on the strict principles of Watson–Crick base pairing. This system can execute various algorithms and tasks using DNA-based

intelligent computing circuits. Nucleic acid intelligent logic operations not only perform precise calculations similar to traditional silicon-based computers but also enable biochemical molecular recognition, sensor analysis, and diagnostic and treatment detection.[70,71] Unlike silicon-based chips, which cannot operate in electrolyte solutions, nucleic acids are biocompatible and water-soluble, allowing them to function effectively in diverse biochemical environments. These advantageous properties make nucleic acids excellent candidates for use in intelligent computing systems. In 1994, Adleman *et al.* proposed that DNA could serve as a model for computational solutions to standard problems in computer science, marking the beginning of DNA computing.[72] Since then, extensive research has focused on nucleic acid intelligent computing. With the aid of parallel computing systems, scientists have demonstrated the significant potential of functional nucleic acid nanotechnology in the field of intelligent computing.[73,74]

DNA is commonly employed as inputs, processing elements, and outputs in the construction of DNA logic gates.[33,75] As inputs, specific sequences of DNA or RNA strands serve as initial stimulus signals. For instance, in strand displacement reactions, a single-stranded DNA (ssDNA) input can trigger a predesigned reaction pathway. For processing, DNA molecules perform logical operations through processes such as hybridization, strand displacement, and enzymatic reactions (*e.g.*, cleavage by endonucleases or ligation by ligases). The computation itself is achieved *via* physicochemical interactions among DNA molecules. As outputs, the results of the computation are typically presented as detectable DNA/RNA signals, such as the generation of a specific fluorescent reporter strand or a conformational change in a DNA structure. As illustrated in Fig. 2a, Song *et al.* developed a DNA-based logic circuit architecture that utilized single-stranded logic gates and strand-displacing DNA polymerase.[76] These logic gates consisted of only a single DNA strand, which significantly reduced leakage reactions and simplified signal recovery steps, thereby improving circuit performance in terms of both computational speed and the number of DNA strands required. Large-scale logic circuits can be constructed through a straightforward cascading strategy.

Traditional DNA computing systems primarily utilize nucleic acid sequences, such as DNA or RNA strands, as inputs, processing units, and outputs within fundamental components like DNA logic gates. However, biological processes in nature are far more complex than merely nucleic acid interactions, involving extensive regulation by non-nucleic acid entities such as small molecules and proteins. Therefore, integrating non-nucleic acid signals into DNA-based computational frameworks is a crucial step in advancing the field from theoretical concepts to practical applications.

To enable these non-nucleic acid targets to operate similarly to nucleic acid strands, synthetic DNA converters can be used to achieve protein-controlled manipulation of dynamic nucleic acid networks.[77] One of the most widely adopted strategies in this context is the use of aptamers, which act as interfaces between various non-nucleic acid targets and nucleic acid-based computations. Aptamers are short nucleic acids (DNA or RNA) selected *via* SELEX (systematic evolution of ligands by exponential enrichment), capable of binding non-nucleic acid targets with high specificity and affinity.[78,79] As illustrated in Fig. 2b, the mechanism relies on the fact that non-nucleic acid ligands do not directly participate in nucleic acid reactions. Instead, when a target ligand (input signal) binds to its corresponding DNA aptamer, it induces a significant conformational change in the aptamer, such as a transition from an unfolded state to a folded state, or *vice versa*. This conformational change is pre-designed within the DNA logic circuit to mimic the introduction of an input nucleic acid strand, thus triggering subsequent strand displacement or assembly reactions.[80,81] In this process, a small molecule or protein input functions similarly to a nucleic acid strand input. The aptamer–ligand binding event effectively replaces traditional nucleic acid hybridization as the new input instruction. This strategy facilitates the efficient and orthogonal transduction of small molecules and proteins, importantly enabling logical and cascaded operations among different ligands.[82] As illustrated in Fig. 2c, Zhang *et al.* demonstrated that conformation-controlled ligand converters could seamlessly integrate various non-nucleic acid molecules, including small molecules and proteins, into nucleic acid computations.[83] This integration enhanced the construction of circuits with greater complexity and scalability, even allowing for algorithmic operations.

Moreover, this strategy can also be applied to perform DNA logic operations using multiple aptamers on living cell membranes for accurate identification of cancer cells,[70,84] or to construct DNA logic-gated nanorobots for multiplexed diagnosis and synergistic therapy.[85] Additionally, aptamer-based strategies can be combined with various nanomaterials to form DNA hybrid structures for highly sensitive detection applications, such as antibiotic monitoring.[86]

2.2.1.1 DNA enzymes (DNAzyme)-based logic computation. Typical biosensing strategies often rely on protein-based molecules, such as antibodies or enzymes. While these methods are effective, they encounter several limitations, including high costs, poor stability, and complex preparation processes. The emergence of DNAzymes has challenged the conventional view of DNA as merely a carrier of genetic information, revealing its additional role as a remarkably efficient catalytic element.[87–89] By harnessing the dual "recognition-catalysis" functionality of DNAzymes, sensing strategies based on these molecules can convert the presence of specific targets, such as metal ions or nucleic acids, into measurable signal outputs, thus providing a novel technological avenue for modern analytical science.

In 2002, Stojanovic *et al.* pioneered a novel logic-gated operation strategy utilizing DNAzymes,[90] capable of executing nucleic acid logic operations for any Boolean function. This groundbreaking work has catalyzed the development of diverse functional nucleic acid logic-gated computing systems. Subsequent innovations have encompassed deoxyribose-based molecular automata,[91] Boolean logic control of aptamer binding states,[92] and advanced intelligent manipulation, including training nucleic acid molecular automata for game-playing applications.[93]

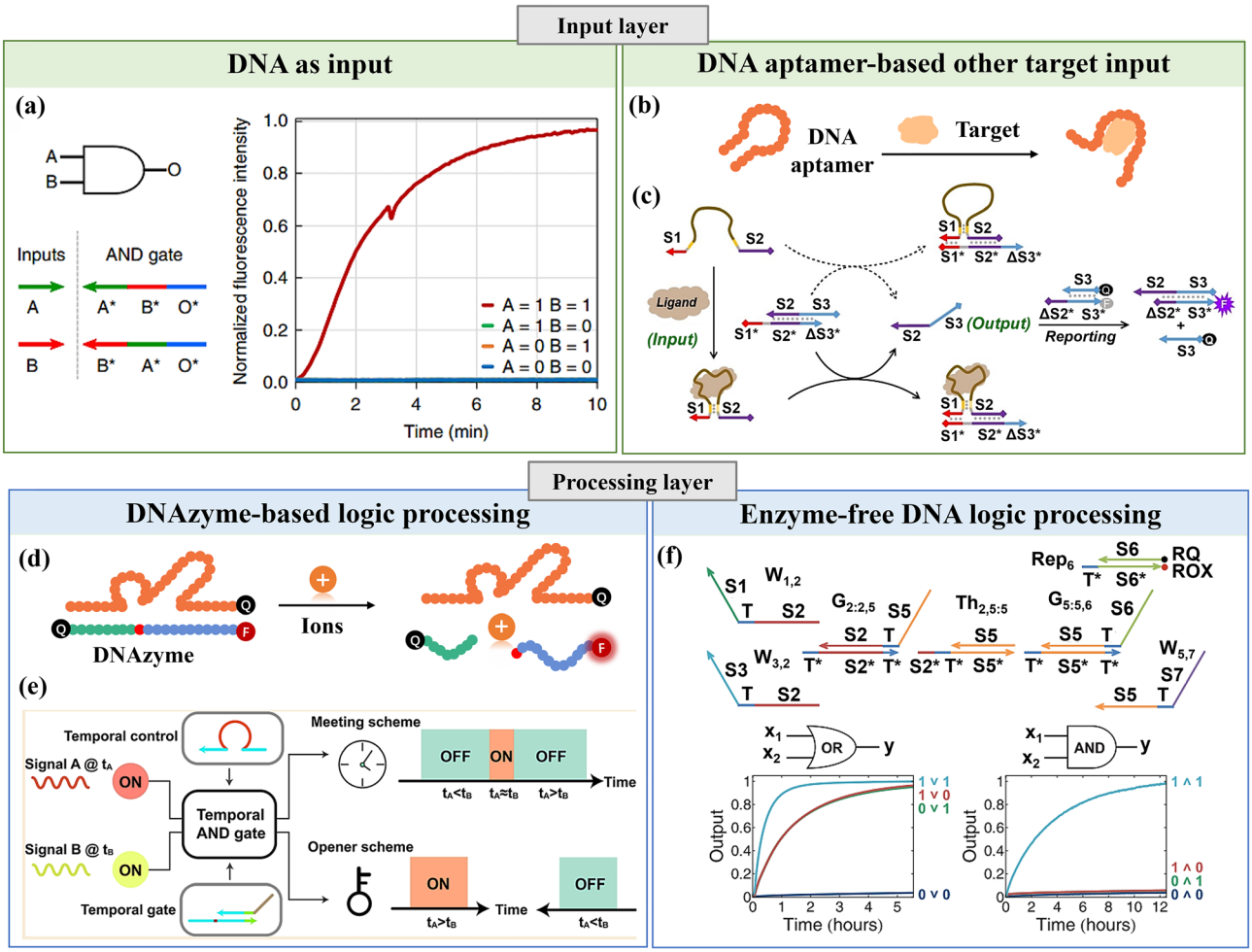


Fig. 2 Construction of the input and processing layers in DNA-based logic computation. (a) Schematic of a single-stranded DNA logic gate circuit utilizing strand-displacing DNA polymerase. Reproduced with permission.[76] Copyright 2019, Springer Nature. (b) Mechanism of DNA aptamer binding and its interaction with target molecules. (c) Schematic illustrating the integration of non-nucleic acid molecules into nucleic acid computing systems *via* nucleic acid aptamers. Reproduced with permission.[83] Copyright 2022, John Wiley and Sons Ltd. (d) Mechanism of the interaction between DNAzymes and target ions leading to sequence-specific cleavage of nucleic acids. (e) A temporal DNA logic gate constructed by DNAzyme-based dissipative DNA strand displacement. Reproduced with permission.[54] Copyright 2024, the American Chemical Society. (f) Enzyme-free strategy for implementing nucleic acid logic circuits and performing logical operations. Reproduced with permission.[39] Copyright 2011, American Association for the Advancement of Science.

DNA logic gates constructed using various types of enzymes can be divided into DNAzyme-based logic gates and protease-based logic gates. DNAzymes are a class of catalytic nucleic acids generated through *in vitro* selection,[94,95] enabling the cleavage of specific substrates in the presence of cofactors. As illustrated in Fig. 2d, DNAzymes are capable of catalyzing a variety of chemical reactions with high efficiency and specificity, similar to protein-based enzymes. One of the most common reactions they facilitate is the cleavage of RNA phosphodiester bonds. The essence of this strategy lies in a system where the substrate strand and enzyme strand are initially separated. The substrate strand typically contains a cleavable ribonucleotide (rA) site. In the presence of a specific target (*e.g.*, Mn^{2+}, Zn^{2+}), the catalytic core of the DNAzyme binds to the target, inducing a conformational change that activates its catalytic function.[87,96] The activated DNAzyme then cleaves the rA site within the substrate strand, resulting in the formation of two fragments. This cleavage event generates detectable physicochemical changes, such as fluorescence emission, alterations in electrical signals, or nanoparticle aggregation, enabling highly sensitive detection of the target.

These DNAzymes possess both enzymatic and DNA properties, which play a crucial role in the development and application of sensing technologies and nanotechnology. Applications include walkers, tweezers, signal amplifiers, logic gates and the composition of dynamic networks (CDN).[94] As shown in Fig. 2e, Hu *et al.* developed a DNAzyme-based dissipative DNA strand displacement (D-DSD) system.[54] In this approach, the input performed a branchpoint-mediated strand replacement reaction, which incorporated the active region of DNAzyme between the branchpoint and the migrating structural domain. The cleavage site for DNAzyme was also included in the substrate ssDNA, activated by a temporal logic gate response. On this basis, two distinct types of temporal logic gates were developed

by combining D-DSD as the foundational elements for temporal control, thereby enabling temporal logic operations and creating a modular, scalable autoregressive memory storage methodology. Liu *et al.* demonstrated an innovative integration of clustered regularly interspaced short palindromic repeat (CRISPR)-DNAzyme with a photoactivation strategy and Boolean logic gates, creating a sophisticated DNAzyme-based imaging probe for sensing and analyzing nuclear metal ions.[95] This system enabled dynamic monitoring of nuclear Zn^{2+} in HeLa cells and mice, showcasing the superior spatiotemporal control capabilities of CRISPR-DNAzyme for advanced imaging applications.

Furthermore, DNAzymes demonstrate remarkable potential for intelligent response control applications. Wang *et al.* reported a significant advancement in cell-specific chemodynamic therapy (CDT) guided by DNAzyme logic gates.[97] They engineered an intelligent nano-machine that utilized DNAzyme logic gates as the control center and metal–organic frameworks (MOFs) as the actuators. In cancer cells, this control center can be activated by high concentrations of microRNA-21 (miRNA-21) and H_2O_2, which subsequently inhibits the expression of catalase, leading to the effective accumulation of H_2O_2. The increased concentration of H_2O_2 further served as an input signal to activate the control center, creating a positive feedback loop that amplified H_2O_2 production within the cancer cells. Upon receiving instructions from the upstream control center, the actuator executed the CDT, converting the over-accumulated H_2O_2 into cytotoxic hydroxyl radicals ($\cdot$OH), which powerfully targeted and eliminated cancer cells.

DNAzyme-based sensing strategies offer several compelling advantages. They demonstrate remarkable catalytic efficiency and robust signal amplification, allowing for highly sensitive detection without the reliance on protein enzymes. These systems also achieve high specificity. Through the rational design of the catalytic core, DNAzymes can effectively discriminate between even closely related target molecules. Additionally, they exhibit superior chemical stability when compared to protein-based enzymes, showcasing resilience to elevated temperatures and degradation. This durability simplifies long-term storage and transportation while ensuring reliable performance under challenging conditions. By merging molecular recognition with effective catalytic signal enhancement, DNAzyme-based sensing represents a significant advancement in biosensing technology. Given their exceptional performance and versatility, these systems hold considerable potential for a wide range of applications in environmental monitoring, medical diagnostics, food safety, and other areas crucial to public health and societal well-being.

2.2.1.2 Enzyme-free DNA logic computation. In the early stages of developing logic-gated molecular cascade reaction systems based on nuclease-driven processes, notable limitations emerged, particularly regarding the efficiency of nuclease cleavage. To overcome these challenges, Seelig *et al.* introduced an enzyme-free nucleic acid logic circuit that employed ssDNA as both inputs and outputs for constructing DNA logic gates.[48] This innovative logic circuit demonstrated capabilities in executing logic operations, cascading, recovery, fan-out, and modularization, effectively reflecting digital design principles. Qian *et al.* further advanced this field by utilizing DNA strand displacement cascades to implement digital logic circuits,[39] experimentally demonstrating various configurations, culminating in a four-bit square root circuit composed of 130 DNA strands. These multi-layered circuits incorporated thresholding and catalysis at each logic operation to facilitate digital signal restoration, achieving fast and reliable performance in large-scale circuits with approximately constant switching times and linear signal propagation delays (Fig. 2f). Subsequently, Srinivas *et al.* also developed an enzyme-free nucleic acid dynamical system,[98] creating a biochemical oscillator that functioned without enzymes or evolved components, instead relying on specially designed DNA molecules within strand displacement cascades. The nucleic acid logic circuit could perform a complete set of Boolean logic functions-AND, OR, and NOT. Moreover, since the input and output took the same form, multi-layer cascades could be achieved. The modular architecture of this system also facilitated integration with a variety of existing molecular components, enabling the construction of a broad and universal nucleic acid-based intelligent logic computing platform.[36,99] Due to the inherent advantages of DNA, such as easy synthesis, low cost, high programmability and excellent biocompatibility, DNA-based enzyme-free computing has emerged as one of the most promising candidates for the next generation of molecular computers, capable of efficiently performing Boolean logic operations.

Enzyme-free DNA logic computing is commonly performed through nucleic acid toehold-mediated strand displacement (TMSD) reactions, which involve the specific hybridization of complementary sequences based on Watson–Crick base pairing for information processing. This TMSD process triggers a cascading strand migration through DNA inputs, enabling multiple nucleic acid site-based ligations. The TMSD process generally consists of three main stages, pivot binding, branch migration and strand dissociation.[100,101] In the TMSD processes, an ssDNA initiated the substitution process by binding to the branched structural domain of the dsDNA, which led to the release of another ssDNA sequence. Due to TMSD's programmable modular responses and excellent biocompatibility, nucleic acid sensors based on TMSD circuits were useful for signal amplification, feedback, cascading, and mode switching.[101] These features make them highly promising for applications in bioanalytical and biomedical research.

By using the TMSD circuits, programmable molecular computing has significantly enhanced the capabilities of cell-free biosensing technology. Jung *et al.* developed a small molecule sensing platform that combined a pivot-mediated TMSD with an *in vitro* transcription interface,[102] serving as an information processing layer. This setup included a ligand-induced activation of the RNA output sensors activated by ligand induction. This platform significantly improved the response speed, achieving a minimum detection time of less than 10 min. Utilizing this principle, TMSD circuits were combined with allosteric transcription factors interface to construct biosensors capable of performing complex logic gate

calculations. This was achieved by layering basic logic components, including NOR, NAND, IMPLY and NIMPLY logic gates. Thus, a multilayer TMSD circuit system similar to the analog-to-digital converter was constructed to produce a series of binary outputs, encoding the concentration range of the target molecule through modeling simulations.

However, system leakage significantly hinders the development of TMSD-based DNA cascade systems that must be implemented sequentially. In order to reduce system leakage in cascade DNA systems, Lv *et al.* designed cascade systems containing two entropy-driven DNA circuits (EDC) processes that operated independently of system leakage caused by unpurified reactants.[103] The authors proposed the "splitting-reconstruction" and "protection-release" strategies, which were used to guide the construction of potential downstream circuit starters derived from upstream EDCs. These strategies enabled the development of cascaded systems that were robust against leakage. The reconstructed downstream circuit starters followed cascade and gate logic principles. Applying these methods, two cascading systems were developed to execute design sequences. The inherent properties of the upstream EDC enhanced the performance of the downstream circuit, improving the signal amplification capabilities of the cascade system for sensitive detection of the corresponding promoter chain. These strategies provided valuable insights for constructing higher-order DNA logic networks utilizing EDC-like circuits.

Efficient analysis of multiple inputs is essential for DNA-based molecular logic computation. To achieve simultaneous analysis of multiple miRNA targets inputs, Miao *et al.* developed an electrochemical platform that combined cascade strand displacement reactions with bipedal walking for the ultrasensitive electrochemical detection of two miRNAs in breast cancer cells.[104] This method prevented strand breaks at the sensing interface and achieved an estimated limit of detection (LOD) of 10 aM. Additionally, the input-triggered cascade strand displacement reaction enabled the construction of various logic gates, including AND, NOT, OR, XOR, NOR, XNOR and XAND, demonstrating the platform's versatility and potential for advanced molecular computing applications.

2.2.2 Synthetic biology-based logic computation. Synthetic biology has emerged as a paradigm for advanced cellular engineering. It enables the development of powerful genetic tools for studying, diagnosing, and treating diseases. Molecular logic computation grounded in synthetic biology employs engineered biomolecules, such as DNA, RNA, and proteins, to create programmable computing systems within living cells or in cell-free environments. These systems replicate Boolean operations (*e.g.*, AND, OR, NOT), similar to electronic logic gates, allowing for precise control over biological behaviors. Central to this discipline is the concept of synthetic biology-based logic computation, which involves embedding computational instructions into natural cellular components to achieve precise regulation of cellular phenotypes.[105,106] By responding to external inputs, including organic or inorganic molecules or light, this approach allows modulation of component functions or their internal control mechanisms, thereby enabling programmable manipulation of biological systems.[107–109]

Synthetic gene networks have been utilized to construct a wide array of biological devices, including logic gates,[14] molecular counters,[110] cell classifiers,[111,112] oscillators,[113] and toggle switches.[110] However, unlike electronic circuit components, which can be electrically and spatially isolated from one another, biological components often interact within the intricate cellular environment and are susceptible to unwanted crosstalk. Limitations in the number and orthogonality of available biological parts hinder the construction of more sophisticated circuits capable of robust operation in living cells. Consequently, designing novel regulatory components that offer broad dynamic range, low crosstalk, and flexible programmability remains highly challenging.

RNA-based regulatory elements present a promising approach to overcoming the challenges associated with controllable gene regulation in synthetic biology.[114,115] Biological components crafted from RNA utilize predictable Watson–Crick base pairing to influence cellular behavior and can be designed with advanced software tools that predict RNA–RNA interactions. Nature has evolved various RNA-based mechanisms that operate at both transcriptional and post-transcriptional levels, making RNA regulators particularly well-suited for logic-driven genetic control in synthetic biology.[115] In computational modules, expressed miRNAs can downregulate transcripts encoding output proteins through RNA interference, enabling logical control of protein expression and thereby supporting diverse cellular functions.

The regulation of RNA-based genetic circuits can be effectively achieved through the use of engineered circular RNAs, which facilitate highly efficient and stable translation in eukaryotic cells.[116] However, while circular interactions are products of natural evolution, creating controllable linear–linear RNA interactions to enhance the dynamic range of riboregulators continues to pose challenges. To tackle this issue, Green *et al.* have developed a novel class of *de novo* riboregulators that facilitated post-transcriptional activation of protein translation.[117] These synthetic riboregulators, known as toehold switches, differentiated themselves from traditional riboregulators by utilizing in vitro-developed toehold-mediated linear–linear interactions to initiate RNA–RNA strand displacement. The versatility, dynamic range, orthogonality, and programmability of toehold switches have established them as a robust platform for sensing and programming the internal states of living cells.

Building on this work, the authors later designed an innovative translation-repressing riboregulator known as the toehold repressor.[118] It utilized robust RNA secondary structures to create inhibitory hairpins through RNA-mediated strand displacement, providing a wide dynamic range that was suitable for precise translational control. This design provided low crosstalk and was suitable for multi-input logic systems. This approach was utilized to create multi-input logic circuits, such as NAND and NOR gates, facilitating logical operations with up to four inputs and introducing innovative tools for programming cellular functions. Following this, Siu *et al.* introduced an

innovative class of riboregulators known as toehold-gated gRNAs (thgRNAs), which incorporated toehold switch elements into the sgRNA scaffold.[119] They demonstrated the programmability of these thgRNAs for multiplexed regulation in *E. coli* with minimal crosstalk. The thgRNAs were designed to utilize TMSD to alter gRNA structure, thereby conditionally controlling Cas9 activity. This technology provided a straightforward "plug-and-play" design framework for orthogonal regulation, allowing various cellular mRNAs to serve as triggers for strand displacement and subsequent modulation of gene expression. Subsequently, Zhao *et al.* also developed an RNA-based eukaryotic toehold switch (eToehold) system that could detect specific RNA sequences within eukaryotic cells and subsequently initiate the translation of a target protein.[120] This eToehold technology, which responded to intracellular RNAs, enabled precise targeting of specific cells, tissues, or organisms and functions as a modular component in the design of intricate genetic circuits, offering significant potential for therapeutic and diagnostic applications.

Constructing complex circuits using RNA-delivered devices within living cells continues to present challenges. Matsuura *et al.* illustrated a synthetic mRNA delivery circuit that integrated RNA-binding proteins for logic computation in mammalian cells.[121] They developed a series of logic gates (AND, OR, NAND, NOR, and XOR) utilizing miRNAs and protein-responsive mRNAs as decision-making controllers to drive transgene expression in response to intracellular inputs (Fig. 3a). Notably, the authors showed that an apoptosis-regulating AND gate sensing two miRNAs could selectively eliminate target cells. Thus, these synthetic RNA-based logic circuits might provide a powerful tool for future therapeutic applications.

Overall, synthetic biology-based logic computation offers a powerful framework for programming cellular behaviors, with broad applications in biotechnology and medicine. By combining modular genetic logic gates, multi-input sensing abilities, and sophisticated gene circuits, this method enables the creation of intelligent cellular systems capable of performing complex tasks with high precision and control.

2.2.3 Nanomaterial-based logic computation. Nanomaterials have garnered significant attention in biochemistry and molecular logic computing, particularly in the development of nucleic acid-based biosensing devices, due to their unique physical and chemical properties. These latter include a large specific surface area, excellent biocompatibility, and superior catalytic performance, which improve the sensitivity and specificity of the sensing methods.[122,123] For instance, lanthanide functionalized MOFs hybrid materials can serve as hybrid materials for logic gate operations, leveraging their multiple luminescence-responsive properties.[124,125] Meanwhile, DNA exhibits attachment capabilities across a diverse range of substrates, including polymers, soft materials, and quantum materials such as polydopamine, hydrogels, microplastics, cellulose nanocrystals, nanodiamonds, and carbon quantum dots.[126] Primary adsorption mechanisms involve π–π stacking, hydrogen bonding, hydrophobic interactions, and metal coordination. Material properties such as surface charge, functional groups, and wettability significantly influence the adsorption and release of DNA, allowing the construction of stimulus-responsive systems. Additionally, by incorporating DNA with nanomaterials and leveraging DNA's excellent programmability and unique interactions with them, the catalytic activity and adsorption performance of nanomaterial-based nanocatalysts

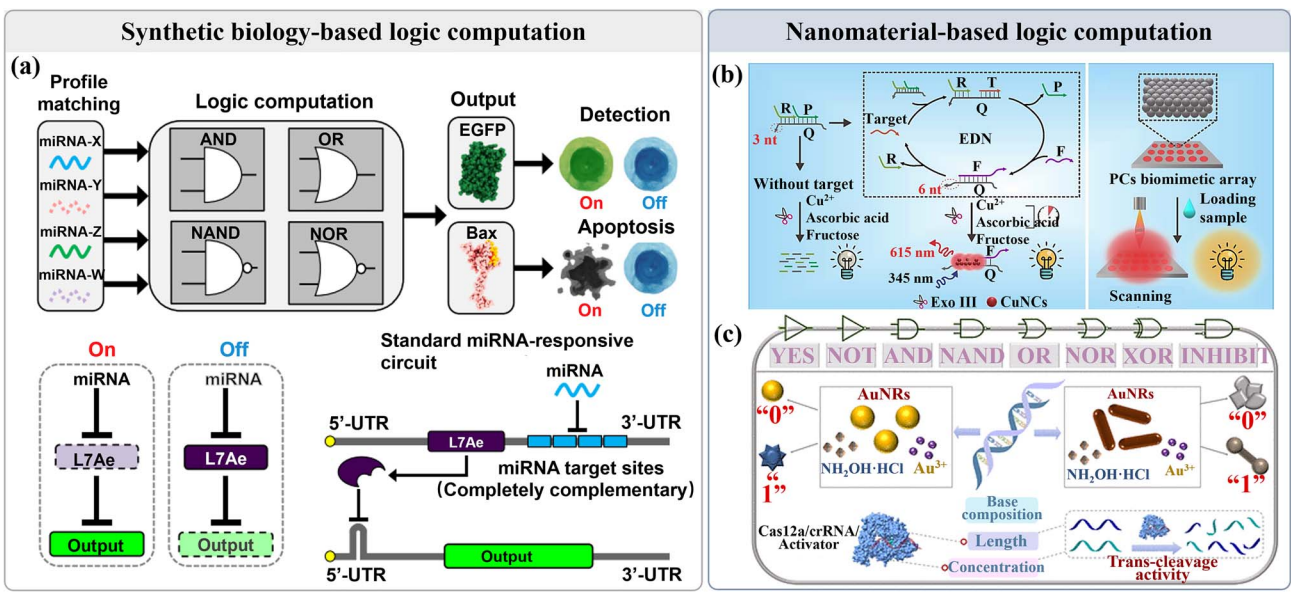


Fig. 3 Different strategies of synthetic biology-based logic computation and nanomaterial-based logic computation. (a) Schematic of synthetic RNA-based logic computation in mammalian cells. Reproduced with permission.[121] Copyright 2018, Springer Nature. (b) Schematic of the preparation and application of smart nanomaterial-based logic entropy-driven nanomachine for high-throughput detection. Reproduced with permission.[128] Copyright 2023, American Chemical Society. (c) Schematic of the DNA molecular computation using the CRISPR-mediated reaction and surface growth of gold nanoparticles. Reproduced with permission.[44] Copyright 2024, American Chemical Society.

can be effectively regulated. This enables valuable functions in nanomaterials-based molecular logic systems.

Programmable DNA circuits can be functionally modified on nanomaterials and rationally designed as artificial molecular catalysts for specific amplification reactions. Pang *et al.* constructed intelligent down/up conversion nanomachines (D/UCNMs) by integrating photosensitizer-designed DNA logic circuits on down/up conversion nanoparticles (D/UCNPs).[127] The DNA logic circuits perform "AND" logic operations in response to dual inputs of tumor-associated glutathione and thymidine kinase 1 mRNAs, thereby initiating enzyme-free TMSD. In addition, the up-conversion luminescence, initially quenched by D/UCNPs, was restored, activating a near-infrared (NIR)-triggered photodynamic therapy (PDT) system with high spatiotemporal precision and enhanced efficiency. Moreover, *in vivo* visual localization of these smart D/UCNMs was achieved utilizing the down-conversion luminescence of D/UCNPs in the second NIR window.

The entropy-driven nanomachine (EDN) can also be integrated with nanomaterials to achieve specific functions in nanomaterial-based logic computation. In a related investigation, Zhang *et al.* developed an EDN that was activated in response to specific targets, subsequently regulating DNA templates and controlling the synthesis of copper nanoclusters (CuNCs) by inhibiting enzymatic cleavage.[128] As shown in Fig. 3b, this innovative approach employed stabilized luminescent CuNCs in conjunction with EDN, utilizing photonic crystals (PCs) as a signal-enhancing substrate array. This strategy enabled the ultrasensitive detection of miRNA-21, achieving high throughput and direct signal readout (96 samples/4 min) with a low LOD of 4.5 pM.[128] By constructing this nanomaterial-based logical EDN, the logical analysis of multiple miRNAs was achieved through "AND" or "OR" logic gating operations. Therefore, the detection method offered several advantages, including being label-free, highly sensitive, flexibly designed, and capable of high-throughput analysis. In an interesting study, Nikitin *et al.* demonstrated the transformation of nanoparticles and microparticles into autonomous biocomputational structures capable of implementing a full set of Boolean logic gates, including YES, NOT, AND, and OR.[129] These logic gates were controlled by input-induced structural disassembly, allowing for applications in targeted cell delivery and advanced immunoassays. To highlight the versatility of this approach, the study also presented a protein-based biocomputing system that operated entirely independently of DNA or RNA, showcasing its adaptability and flexibility. This comprehensive exploration emphasizes the transformative potential of nanomaterials and DNA-based systems in advancing nucleic acid detection, molecular logic gates, biocomputing, diagnostic and therapeutic applications.

In contrast to traditional nanomaterial-based logic gates that primarily rely on catalytic effects as variable fluorescence outputs, Guo *et al.* pioneered the use of the catalytic reaction of DNA-silver nanoclusters (AgNCs) as an output signal.[130] The established DNA/Ag NC-based nanocatalysts were useful in the construction of molecular logic gates. Moreover, as illustrated in Fig. 3c, Fu *et al.* constructed a series of logic gates, including YES/NOT, AND/NAND, OR/NOR, XOR and INHIBIT, through the DNA-mediated growth of gold nanomaterials.[44] These fundamental logic operations were later employed to create an OR-2 to 1 encoder, a parity checker, and a Gray (G) code encoder as a reflected binary code encoder. These developed biological computing systems provided remarkable benefits, including simplicity, fast, and label-free functionality and possess great potential for revolutionizing information processing.

3 Functionalities of intelligent logic-gated toolkits

3.1 Modular multi-signal integration

Modular multi-signal integration is essential for sophisticated multiple-target sensing, particularly when instruments have limitations that restrict them to detecting only a limited number of signals. Consequently, it becomes necessary to make logical integration judgments regarding multiple signals to streamline output procedures and signal processing. This modular multi-signal integration approach serves as an intelligent simplification strategy for logical operations, enabling precise temporal responses to multiple inputs, processing and integrating biological signals from various signaling domains, and programmatically executing corresponding functional responses.[131–133] This methodology is widely utilized for signal perception, integration and actuation in complex environments. It is of critical importance in the fields of gene regulation, precise identification of cell types, cell therapy, and diagnosis and treatment of disease.

Kang *et al.* designed a multi-input Boolean logic computational conditional guide RNAs (cgRNAs) to achieve orthogonal regulation of endogenous gene expression.[134] By leveraging the dynamic tunability of cgRNA design, two-input AND, OR, NOT logic gates and three-input A OR (B AND C) logic operations were achieved (Fig. 4a). This approach allowed for precise regulation of target gene expression for enzymes, transcription factors, and cytoskeleton-associated proteins. This cgRNA design strategy exhibited a broad dynamic range and the ability to process complex intracellular logic operations.

Based on the TMSD reaction, DNA strand displacement-based AND logic gates can be designed to achieve intelligent multi-target analysis, facilitating accurate cell identification. Li *et al.* designed an anemone-like DNA nanomachine utilizing TMSD reaction, comprising two YES gates and one AND gate, for simultaneous detection of multiple cellular targets.[135] This nanomachine integrates different types of logic gates-think of them as decision-making processes-allowing it to work effectively with various signals. As a result, this technology can quickly and accurately identify tumor cells, which is essential for early diagnosis and treatment of cancer. Chang *et al.* have created a device that worked like a smart switch on living cell surfaces using a joint pivot formation approach. This device used a clever approach to activate multiple pivot regions by initiating a hybridization chain reaction (HCR) process in a programmed and timed manner, ensuring accuracy and specificity in cell recognition.[84] The fully modular components

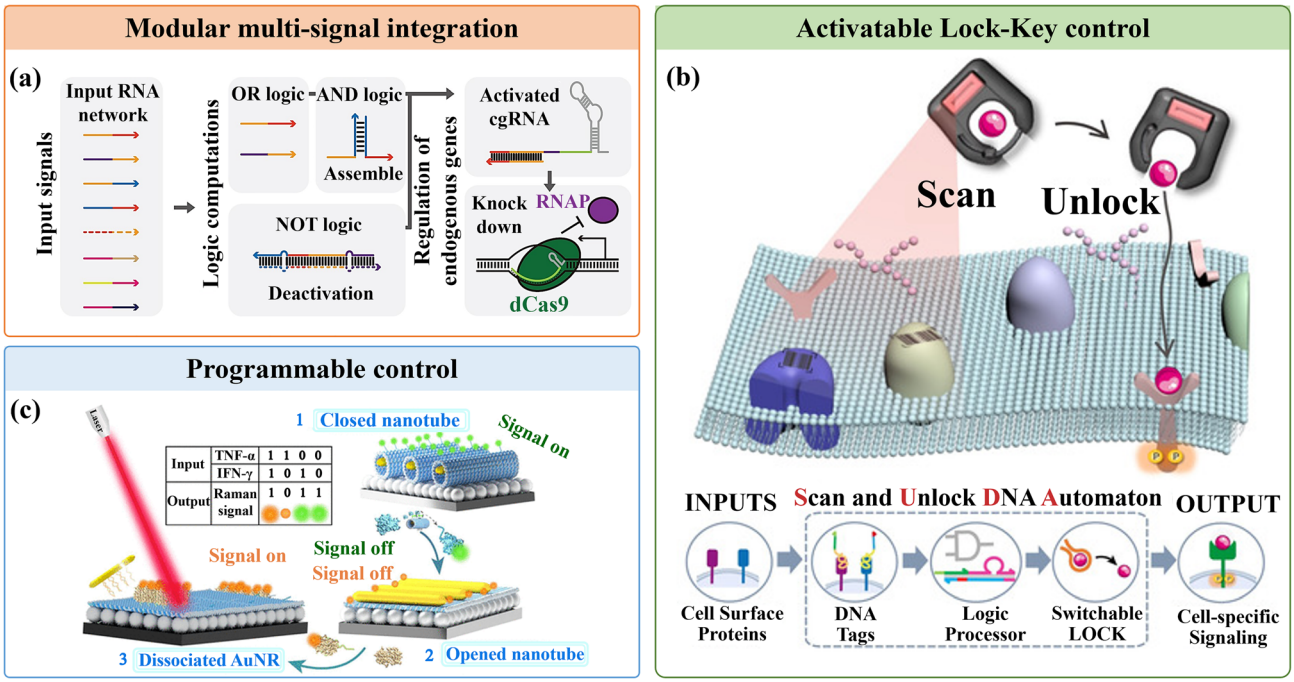


Fig. 4 Functionalities of intelligent logic-gated toolkits. (a) Schematic of the logical regulation of endogenous gene expression using a modular multi-input processing strategy. Reproduced with permission.[134] Copyright 2024, Oxford University Press. (b) Schematic of the lock-and-key controlling strategy for cell-specific modulation of ligand–receptor interaction. Reproduced with permission.[143] Copyright 2020, John Wiley and Sons Ltd. (c) Schematic of a DNA origami plasmonic nanoantenna for programmable SERS sensing of multiple cytokines in cancer immunotherapy. Reproduced with permission.[150] Copyright 2024, the American Chemical Society.

allowed for scalability through multiple fulcrum combinations, enabling logical calculations based on various cell markers. Additionally, Cho and colleagues developed a programmable SUPRA CAR system that enhanced tumor specificity through logical responses to multiple antigens.[136] The modular design of this system permitted easy redirection of target specificity and adjustment of T cell activity, enabling independent control of different signaling pathways and cell types. By integrating these signaling pathways into a single system, the effectiveness and safety of CAR T-cell therapy were improved, making it a more reliable cancer treatment.

To integrate three or more inputs, Kempton *et al.* developed a highly programmable, spontaneously reconfigurable split-type Cas12a system for signal integration. This system worked like a series of switches, implementing robust two, three, and four inputs for scalable AND gates to control endogenous genes.[137] By combining these signals, the system can be used to help guide treatment decisions, acting as a central platform for developing new technologies that respond to cancer-related information.

3.2 Activatable lock–key (OFF–ON) reconfigurable control

Activatable lock-and-key (OFF–ON) reconfigurable control systems play a pivotal role in advancing biochemical research, particularly in elucidating complex biomolecular interactions. These systems offer several critical advantages, including precise molecular recognition and regulation, conditional activation and response mechanisms, dynamic regulatory capabilities, significant reduction of background noise with enhanced fault tolerance, cell-specific recognition enabling targeted therapeutic interventions,[18,138,139] implementation of sophisticated biological logic operations, and real-time monitoring coupled with feedback control mechanisms.

The activatable lock-and-key reconfigurable control represents an advanced molecular mechanism that operates through conditional, trigger-dependent activation. This system utilizes intra- and extracellular or cell-surface inputs as molecular keys while employing DNA- or aptamer-encoded logic gates as corresponding locks. These molecular locks undergo structural reconfiguration upon specific activation events, enabling them to respond to diverse biological cues. This sophisticated mechanism facilitates precise, context-dependent biological responses, making it particularly valuable in complex biological systems and therapeutic applications.

The lock–key strategy can achieve accurate molecular recognition and regulation. For the detection of biochemical targets secreted by cells into *in vitro*, Wang *et al.* proposed a double-locked probe mediated catalytic hairpin assembly (CHA) for logical detection of miRNA and apurinic/apyrimidinic endonuclease 1 (APE1).[140] Each CHA hairpin contained a lock, with APE1 serving as the first key to unlock and miRNA as the second key. The system required the presence of both keys to unlock the hairpin, triggering a self-assembly reaction that produced a fluorescent signal. This dual-lock biosensor exhibited low background noise and high sensitivity and specificity, making it a robust tool for biochemical detection. Ren

et al. also designed a double-lock key system that activated two recognition elements on the target cell membrane before delivering small interfering RNA (siRNA), effectively controlling the cell's "lock-open" state.[141] The system significantly improved delivery specificity, avoided off-target toxicity, and achieved specific cell subtype recognition and precise delivery of siRNA.

The lock–key strategy can also realize complex biological logic operations. Nikitin *et al.* demonstrated the transformation of nanoparticles or microparticles into autonomous biocomputational structures capable of implementing a fully functional set of Boolean logic gates (YES, NOT, AND, and OR).[129] These structures were logically gated by input-induced structural disassembly, enabling logically-gated cell targeting and advanced immunoassay.[85] The biocomputational structures were based on stimulus-responsive composite nanoparticle/biomolecular interfaces, which can target a wide range of entities, from solid-bound molecules to nanoparticles and living cells. This diverse mode of operation enabled complex information processing and targeted biological interventions.

The activatable key-locked (OFF–ON) reconfigurable control strategy not only conducts in responds to complex signals with logical reliability but also selectively regulates cellular behavior, which is crucial for cell therapy. In terms of techniques for tracking macrophage movement, Fernandez *et al.* introduced a fluorescent-activated C–C motif chemokine ligand 2 (CCL2) chemokine, enabling *in vivo* imaging of active transfer-associated macrophages through the "AND" gate strategy.[142] Unlike previous methods that relied on fluorescently labeled antibodies and always-on fluorescent chemokines, this strategy ensured that fluorescence was released only after receptor binding and intracellular activation, thereby achieving high specificity.

Douglas *et al.* described an autonomous DNA nanorobot controlled by aptamer-encoded logic gates, capable of delivering signaling molecules to the cell surface for conditional, triggered activation.[138] The nanorobot reconfigured its structure for signaling and was able to collect flagellin from solution, inducing enhanced T cell activation. This suggests that the activatable lock-and-key reconfigurable control strategy can induce multiple modifiable changes in cell behaviour, highlighting its potential for therapeutic applications. As illustrated in Fig. 4b, our group designed an intelligent "Scan and Unlock" DNA automaton system that used DNA-based cell surface CRNs to scan and evaluate the molecular profile of proteins on the cell surface *via* Boolean logic circuits.[143] This system selectively activated protein-ligands to interact with homologous receptors on their target cells, modulating cell-specific signaling and behavior. This strategy enabled the design of highly cell-selective protein ligands that regulate cell behavior, providing a programmable, scalable, and universal paradigm for cell-specific therapy with minimal side effects.

3.3 Programmable control

Logic-gated programmable bioanalytical strategies represent a cutting-edge approach in bioengineering and biosensing, allowing for the creation of sophisticated, context-dependent systems for biological analysis and intervention. These strategies harness the principles of Boolean logic and molecular programming to develop highly specific and tunable biological circuits, offering transformative potential in both fundamental research and applied sciences. Logic-gated systems employ molecular components, such as DNA, RNA, proteins, or synthetic molecules, to function as biological logic gates (*e.g.*, AND, OR, NOT). These gates interpret specific input signals, such as biomarkers or cellular signals, and produce precise outputs, including signal transduction or therapeutic actions.[144–146] The programmability of these systems facilitates the integration of multiple inputs and enables the execution of complex decision-making processes at the molecular level.

Programmable DNA circuits are artificially engineered systems based on molecular self-assembly and dynamic interactions of DNA, capable of emulating the functions of electronic logic circuits to perform computation, signal processing, and decision-making at the molecular level. Their core functionality leverages DNA's programmability, high specificity, and massive parallelism to enable sophisticated biomolecular information processing. Programmable control enables the design and programming of various logic circuits capable of recognizing complex multi-signal inputs and regulating cellular behavior with high precision. Chen *et al.* developed a set of logic gates (YES, NOR, AND, OR, AND/OR) that respond to multiple inputs by employing aptamer recognition and proximity-induced DNA assembly.[147] They designed aptamers as "robotic arms" to capture target receptors (c-Met and CD71) and facilitate DNA-induced receptor assembly. This approach allowed for the programmable regulation of cell signal transduction and behavior. This modular design and construction of DNA-based logic gates enabled the programmable control of layered circuits, providing sophisticated computational control over receptor organization and function.

Tian *et al.* introduced a programmable vector-cyclic single-stranded DNA (CssDNA) for gene expression in a yeast-based cell-free protein expression (CFE) system.[148] The positive and antisense CssDNA had distinct protein expression pathways. By designing and constructing dual-input logic gates using CssDNA as a logic unit, they validated the feasibility of CssDNA as a programmable vector for gene regulation in CFE systems. This study enhanced the understanding of how CssDNA can be utilized for programmable gene expression and regulation, thereby expanding the synthetic biology toolkit.

Programmable remodelling of the cell surface enables logical control of cell behaviour. Qu *et al.* constructed a series of DNA-based logic gates (AND, OR, XOR, AND AND-OR) to program mammalian cell adhesion and achieve high-precision regulation of cell behavior.[149] The modular design of DNA-based logic gates enabled the engineering of complex hierarchical circuits, allowing for advanced computational control of mammalian cell adhesion. The mechanism of DNA-based CRNs, which relied on sequence recognition and strand displacement reactions, provided a versatile and programmable tool for the logical control of mammalian cell behavior with high accuracy and predictability.

Surface-enhanced Raman spectroscopy (SERS) offers significant advantages over fluorescence spectroscopy in identifying trace substances due to the signal enhancement provided by plasma nanostructures. The assembly of equipartitioned excitonic nanostructures using programmable DNA origami enables multiple detection in practical applications. As shown in Fig. 4c, Tang *et al.* constructed a novel stimulus-responsive DNA origami plasmonic nanoantenna, implementing a complete set of Boolean logic gates using cytokine molecules as inputs and changes in Raman signals as outputs.[150] These logic gates included AND, NOT, OR, NOR, XOR, XNOR and INHIBIT gates, achieving programmable SERS-based multiple biosensing of cytokines in cancer immunotherapy. Future development of logic-gated programmable bioanalytical strategies may include incorporating AI to optimize circuit design, exploring new molecular components for enhanced functionality, and translating these systems into clinical and industrial applications.

3.4 Logic-gated nanomachines

Logic-gated nanomachines are artificially engineered nanosystems designed to perform molecular logic operations, enabling them to execute programmed responses when they encounter specific combinations of biological signals. These sophisticated systems have emerged as a cutting-edge area of research, due to their pivotal roles in disease diagnostics, precision therapeutics, and real-time *in vivo* monitoring.[138,151,152]

These nanomachines perform critical functions, starting with molecular-level conditional decision-making through Boolean logic gates (AND, OR, NOT). Their operation requires co-activation by specific biomarkers (*e.g.*, miRNAs, proteins, pH changes, or enzymes) to minimize false-positive signals in diagnostic applications. A notable example is the autonomous DNA nanorobot developed by Douglas *et al.* (Fig. 5a),[138] which demonstrated three key capabilities: (1) the transport of molecular payloads to target cells, (2) sensing of cell surface inputs for conditional activation, and (3) structural reconfiguration for accurate payload delivery. This programmable device allowed for the loading of various therapeutic materials in a highly organized manner and was controlled by aptamer-encoded logic gates, enabling a response to multiple molecular cues. The system employed several distinct AND-gate operations and demonstrated effectiveness in selectively controlling the functions of the nanomachine, and can be utilized in precision cell-targeting therapies.

Additionally, these nanomachines demonstrate a dynamic ability to respond to changes in their microenvironment, such as hypoxia, reactive oxygen species (ROS) levels, and adenosine triphosphate (ATP) concentrations. This responsiveness enables targeted actions at pathological sites, including tumors and inflamed tissues. Liu *et al.* engineered an innovative class of logic-gated plasmonic nanodevices by co-assembling two gold nanorods (AuNRs) with computational elements on a tweezer-shaped DNA origami template (Fig. 5b).[153] Upon recognizing a variety of molecular inputs, such as DNA strands, glutathione, or adenosine, these nanostructures underwent programmed geometric reconfiguration, resulting in corresponding changes in the circular dichroism (CD) signals of the plasmonic AuNR-origami assemblies. This platform successfully executed a complete set of modular Boolean logic operations (YES, NOT, AND, OR) and was further developed to create a sophisticated three-input circuit capable of performing combined OR–NOT–AND Boolean computations. This DNA-based self-assembly approach highlights significant potential for programmable applications across fields such as photonic modulators, molecular information processing, and bioanalytical systems.

Moreover, these nanomachines exhibit cascading response capabilities that amplify and transduce subtle biological signals into measurable outputs (*e.g.*, fluorescence, electrochemical signals), thereby achieving a significant enhancement in detection sensitivity. For example, Wang *et al.* developed a genetically intelligent DNA nanorobot (Fig. 5c),[152] which was precisely engineered to execute coordinated responses to both intercellular and intracellular microenvironmental cues. This innovative system facilitated lysosome-targeted payload delivery, markedly improving therapeutic efficacy through subcellular-level interventions in tumor treatment. Such logic-gated DNA nanorobots showcase extraordinary potential for modulating cellular functions and advancing applications in precision medicine. Expanding on these capabilities, logic-gated nanomachines present particularly promising platforms for point-of-care diagnostic systems as well as dynamic *in vivo* therapeutic applications, as thoroughly discussed in Section 5.5.6.

4 Analytical sensing strategies based on intelligent logic-gated operations

4.1 Fluorescent strategies

Fluorescent sensors are analytical devices that convert analyte signals into fluorescent signals as outputs. These sensors utilize various reporter modules, including chemically synthesized fluorophores,[154] nucleic acid-based probes,[155–157] metal–organic skeletons,[158] quantum dots,[159] nanoparticle-based probes,[160] and genetically engineered fluorescent proteins.[161] The integration of DNA logic computation with fluorescent biosensors has significantly advanced the bioanalytical field, facilitating the development of multi-sensing platforms that offer user-friendly, rapid, and precise diagnostic analyses with exceptional sensitivity and specificity.

The main challenge of fluorescence sensing is the limitation of the fluorescence channel in multi-color fluorescence. To address this challenge, implementing logical operations can transform the fluorescence signal into a reprogrammable and independent readout for the sensing system. Xiao *et al.* developed self-luminous carbon dots (CDs) that emit blue (CD-1), green (CD-2), and red (CD-3) fluorescence.[162] As shown in Fig. 6a, these CDs were designed to perform various logic operations, including NOT, NAND and NOR. Furthermore, the logical outputs resulting from these logic operations were encoded into quick response codes, which could be readily scanned and decoded with a smartphone. This strategy

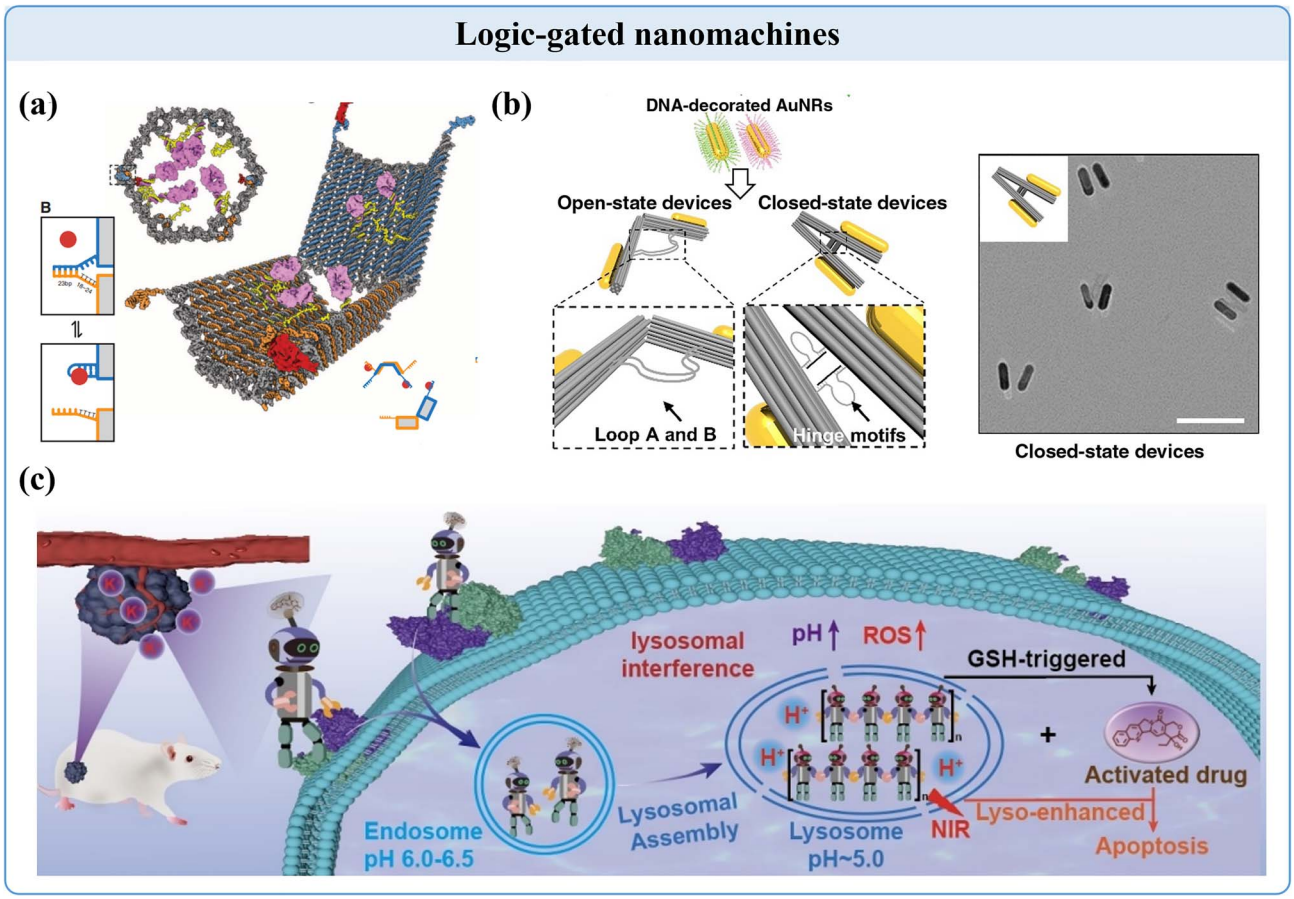


Fig. 5 Functionalities of logic-gated nanomachines. (a) Schematic of a logic-gated nanorobot for targeted transport of molecular payloads. Reproduced with permission.[138] Copyright 2012, the American Association for the Advancement of Science. (b) Schematic of logic-gated plasmonic nanodevices based on DNA-templated assembly. Reproduced with permission.[153] Copyright 2021, the Chinese Chemical Society. (c) Schematic of logic-gated intelligent DNA nanomachines engineered for cascade responses, targeted cargo delivery and enhanced cancer therapy. Reproduced with permission.[152] Copyright 2025, John Wiley and Sons Ltd.

established a robust framework for multi-level logical operations and provided a user-friendly and accessible readout system for molecular computing applications. Wang *et al.* proposed a molecular logic-gated fluorescent probe P_0-pH-SO_2 for dual-channel simultaneous detection of sulfite and pH changes in mitochondria.[163] This fluorescent molecular logic gate probe was rapidly activated by mitochondrial sulfite, resulting in the emission of green fluorescence, while red fluorescence was simultaneously quenched by mitochondrial protons. This study introduced a logic-gated molecular probe, offering a versatile strategy for monitoring the roles of sulfite and H^+ in cuproptosis.

Genetically encoded fluorescent sensors are transformative tools that convert chemical and physical signals into optical signals, enabling the visualization of physiological processes in living cells and freely moving animals. These sensors predominantly employ fluorescent proteins as their reporter modules.[164] Chen *et al.* presented a novel approach for designing logic gates capable of regulating protein binding.[165] These gates were constructed from engineered small proteins, which shared structural similarities but were designed with specific interaction modules. By utilizing monomers and covalently linked monomers as inputs, the authors successfully developed 2-input and 3-input logic gates based on competitive binding mechanisms. Vishweshwaraiah *et al.* conducted an engineered single-protein system designed to function as a "two-input logic OR gate" through allosteric regulation.[166] This system enabled orthogonal control of protein function using chemical and optogenetic switches. This study established a proof of principle for the precise multimodal regulation of protein function and laid the groundwork for the development of sophisticated nanoscale computational agents.

For fluorescence sensing, signal amplification strategies significantly improved the sensitivity and detection capabilities. Among various amplification methods, CHA shows the unique advantages of programmable design, ease of operation, time-saving and low cost, as well as a strong ability to amplify signals efficiently under *in vitro* and *in vivo* thermostatic conditions. Luo *et al.* summarized the application of CHA as a cascade nucleic acid circuit in fluorescent biosensors.[167] Deng *et al.* developed a logic gate biosensing platform by integrating CRISPR-Cas12a with CHA for the detection of polychlorinated biphenyls.[168] The output signal of this platform was visually observable under ultraviolet light. This biosensing platform

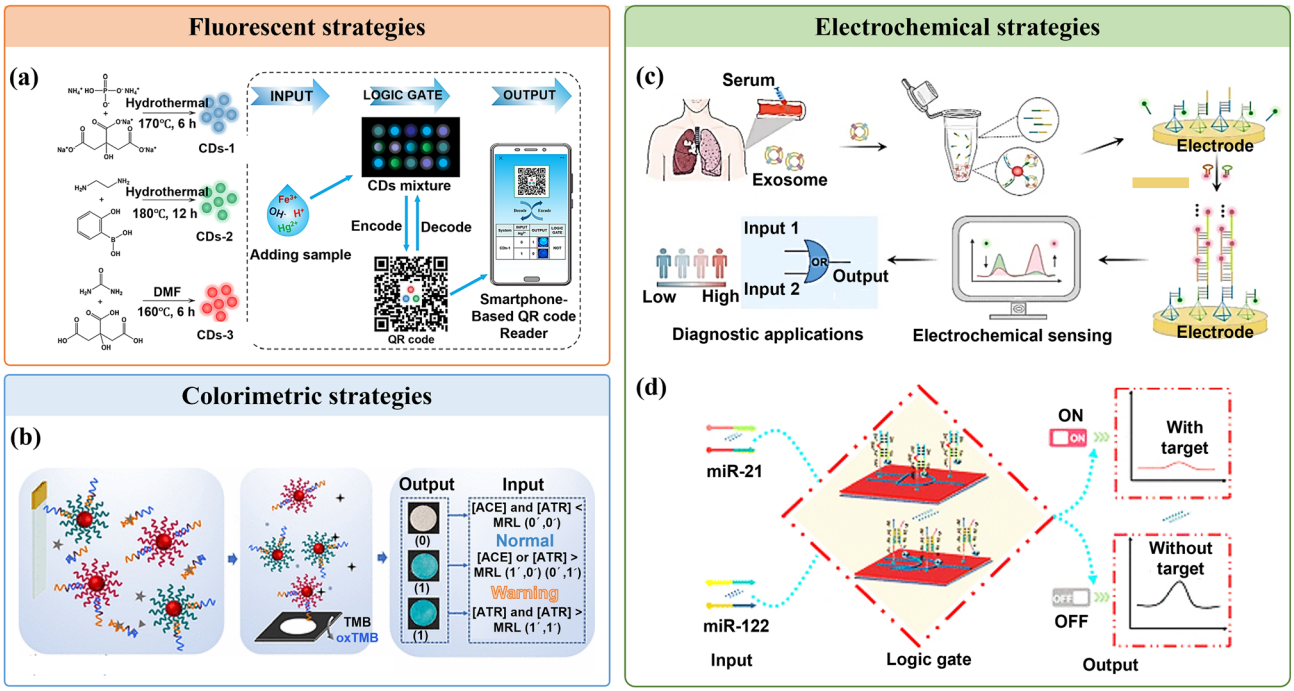


Fig. 6 Different analytical sensing strategies based on intelligent molecular logic-gated computing operations. (a) Schematic of multicolor fluorescent carbon nanodots logic design for smartphone-based information extraction. Reproduced with permission.[162] Copyright 2021, American Chemical Society. (b) Schematic of the composition of the DNA logic gate for intuitive assessment of chemical contaminant exceedance by colorimetric strategy. Reproduced with permission.[177] Copyright 2024, American Chemical Society. (c) Schematic of a ratiometric electrochemical OR gate assay for the detection of NSCLC-derived exosomes. Reproduced with permission.[183] Copyright 2024, Springer Nature. (d) Schematic of an electrochemical biosensor integrated with a logic circuit as an intelligent automaton for two-miRNA detection. Reproduced with permission.[187] Copyright 2024, The Royal Society of Chemistry.

demonstrated significant advantages, including versatile input combinations, intuitive digital output, and high flexibility and scalability, making it a promising tool for the intelligent and efficient detection of polychlorinated biphenyls.

DNAzyme-based amplification also offers significant advantages such as high specificity and design flexibility for fluorescence sensing, making it a powerful tool in bioanalytical applications. Pan *et al.* developed an ultrasensitive fluorescent biosensor for the detection of Cd^{2+} by leveraging a Cd^{2+}-driven wheel walker deoxyribonuclease.[169] This sensor exhibited a linear detection range from 1 pM to 10 nM and an LOD of 0.2 pM. The sensor utilized a Cd^{2+}-specific deoxyribonuclease for heavy metal ion recognition. Upon activation by Cd^{2+}, the deoxyribonuclease traversed a DNA track *via* a TMSD reaction, leading to successive cleavage of BHQ-Cy5-modified substrate strands and generating a high fluorescence signal.

To improve the anti-interference capability and self-calibration functionality of fluorescence sensing, ratiometric fluorescence sensors are commonly designed for implementing logic-gated molecular operations in fluorescence-based detection systems.[170] Ratiometric fluorescence sensors offer the advantages of visual detection, interference tolerance and higher sensitivity than single-emission fluorescence sensors.[171] Tian *et al.* developed a ratiometric fluorescence aptamer sensor for sensitive detection of kanamycin (KAN) using fluorescence and colorimetric signals.[172] CuNCs encapsulated in SiO_2 ($CuNCs@SiO_2$) were used to enhance stability and maintain bright blue fluorescence as a reference signal. DNA-templated silver nanoclusters (DNA-AgNCs), synthesized using DNA strands containing KAN aptamers, served as the response signal for red fluorescence. The presence of KAN induced fluorescence signal changes, resulting in visual color alterations. The aptasensor demonstrated LODs of 7.3 nM and 14.5 nM for ratiometric fluorescence and colorimetric modes, respectively, and was effectively applied for quantitative measurement of KAN in food samples. Hou *et al.* fabricated a MOF nanozyme-based ratiometric fluorescence sensor for the intelligent recognition and detection of sarcosine, utilizing an AND-(AND^NAND) contrary logic circuit.[173] This sensor demonstrated commendable performance in human serum samples, and further advancements enabled smartphone-based portable sensing of sarcosine through ratiometric RGB analysis, advancing the field of point-of-care analysis.

4.2 Colorimetric strategies

Colorimetric methods are increasingly favored for field diagnostics due to their operational simplicity, cost-effectiveness, practicality, and visual result output. Colorimetric sensors that utilize logic-gating intelligent arithmetic strategies can process multiple inputs and visualize output signals through Boolean logic operations. This approach provides a versatile solution to deal with different situations of analytes. Moreover,

the programmability of logic gates allows the flexible design of custom logic systems tailored to specific detection needs. For example, Ge *et al.* demonstrated a novel approach by visualizing output signals from a 3D DNA walker.[174] This system successfully detected SARS-CoV-2 RNA fragments at concentrations as low as 1 nM. The DNA walker unsealed the walking strand in the presence of both ORF1ab and NRNA fragments, cleaving the track strand during the walk. As the walking process proceeded, the decrease in negative charge density and the weakening of spatial repulsion caused the DNA walker to aggregate at high salt concentrations. This aggregation led to a visible color change from red to purple, permitting easy interpretation of the results. In another study, Borah *et al.* developed a logic gate biosensor for colorimetric detection of thiocyanate.[175] This system utilized Cu^{2+} and thiocyanate as inputs, which were composed of a silver-based colloidal plasmonic nanosensor, to form an AND logic gate. The biosensor exhibited a detection range of 100 nM to 1.0 μM for thiocyanate with an LOD value of 53.60 nM.

To detect multiple nucleic acid targets simultaneously in one detection, Gong *et al.* developed a CRISPR/Cas12a-based biosensing platform utilizing AND logic gates for the highly sensitive colorimetric detection of dual miRNAs.[176] This innovative strategy facilitated the simultaneous identification of two target miRNAs through CRISPR-Cas12a and a single crRNA, eliminating the need for complex nucleic acid amplification procedures or sophisticated instrumentation. Notably, the colorimetric response induced by target miRNA concentrations as low as 1 pM was discernible by the naked eye, while the instrumental LOD was an impressive 36.4 fM. The platform successfully detected the overexpression of miRNA-205 and miRNA-944 in clinical human serum samples, enabling reliable discrimination between lung cancer patients and healthy individuals. Current molecular logic gates primarily focus on qualitatively assessing the presence of target substances, which poses limitations in situations that require quantitative analysis, such as monitoring chemical pollutants. To address this gap, Wang *et al.* have developed a novel type of DNA logic gate with an adjustable threshold, specifically designed to overcome the challenges posed by pollutants.[177] As shown in Fig. 6b, the core of this logic gate was a DNA-gold nanoparticle (AuNP) hybrid film that incorporated an aptamer selectively binding to acetamiprid and atrazine. Upon interaction with these pollutants, the film degraded and released AuNP, which then catalyzed the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB) in the presence of Hg^{2+}, producing a visible blue color on the test paper. This method enabled a semi-quantitative evaluation of pollutant levels and provided clear visual feedback regarding excessive contamination.

Given that colorimetric methods facilitate on-site diagnostics without the need for sophisticated instrumentation, while fluorescence-based methods offer quantitative and highly sensitive detection, biosensors integrating fluorescence-colorimetric dual-mode detection have gained significant attention in analytical applications. For example, Choi *et al.* pioneered a nucleic acid amplification-free biosensor based on CRISPR-Cas12a, capable of detecting breast cancer gene-1 within 30 min.[178] This system permitted visual detection of cell-free DNA in the nanomolar range, while metal-enhanced fluorescence enabled quantification of target concentrations from 1 fM to 100 pM. Rong *et al.* developed a colorimetric and fluorescent dual-signal readout method based on AND logic gates for the detection of tetracyclines (TCs).[179] This system achieved LODs of 83.3 nM and 21.9 nM, respectively. In this design, AuNPs, commonly used in colorimetric detection, were released through the etching of the MnO_2 shell layer in the presence of TCs, resulting in a visible color change.

Additionally, Han *et al.* engineered SiO_2@Au/QDs with dual functionality for colorimetry and fluorescence, integrating them into a novel biosensor for lateral flow immunoassay.[180] This biosensor achieved LODs of 1 ng mL^{-1} and 33 pg mL^{-1} for colorimetric and fluorescent modes, respectively. The biosensor had the advantages of a simple synthesis method, low cost, and possibility of mass production, which can be effectively applied to those resource-poor areas that lack advanced testing personnel and equipment.

4.3 Electrochemical strategies

Electrochemical sensors incorporating logic-gated intelligent arithmetic strategies have garnered significant interest due to their unique integration of the high sensitivity of electroanalytical techniques with the programmable versatility of nucleic acid molecules.[181,182] These sensors leverage specific biomolecular recognition events to process multiple signal inputs through logical operations, converting biochemical targets into measurable electrical outputs. The synergy between highly sensitive electrochemical methods and programmable nucleic acid interactions endows these biosensors with advantageous features, including rapid detection, operational simplicity, cost-effectiveness, minimal sample requirements, and portability, making them highly promising for clinical diagnostics.

Meng *et al.* developed an innovative ratiometric electrochemical biosensor integrated with an OR logic gate for surface protein profiling of exosomes derived from clinical serum samples.[183] As shown in Fig. 6c, by utilizing specific aptamers to identify clinically validated biomarkers, the assay demonstrated the ability to ultrasensitively detect trace levels of non-small cell lung cancer (NSCLC) derived exosomes within complex serum samples. This method performed the analysis of six serum biomarkers in the accurate diagnosis, staging, and prognosis of NSCLC, achieving a diagnostic sensitivity of 93.3%, even at the early stage. This assay provided an advanced tool for exosome quantification and promoted exosome-based liquid biopsy for clinical cancer management.

To achieve ultrasensitive detection of trace nucleic acids in complex samples, various signal and nucleic acid amplification strategies, such as HCR and ligase chain reaction (LCR), are commonly utilized. For example, Zhu *et al.* pioneered the integration of two-dimensional (2D) nanomaterial-nucleic acid interactions with electrochemiluminescent resonance energy transfer to develop DNA-based molecular logic gates.[184] The innovative approach allowed for the quantification of miRNA-133a through a ratiometric measurement, achieving a low

LOD of 0.41 pM. A significant challenge in real-sample electrochemical biosensing is the fouling of electrode surfaces by interfering substances, such as proteins and sulfur-containing compounds. To tackle this issue, Yang *et al.* introduced a split strategy to separate the recognition process from the signal detection step, effectively avoiding contaminant-induced degradation of the sensing layer and maintaining the fidelity of electrochemical signal transduction.[185] This system was applied to the early diagnosis of chronic granulocytic leukemia and minimal residual disease (MRD) monitoring, achieving an ultra-low LOD of 1 aM for BCR/ABLp210 transcripts. The method had the advantages of low consumption, simplicity, and miniaturisation, which enabled the monitoring of MRD at an ultralow level and facilitated on-site diagnosis for point-of-care clinical applications.

The advancements in nucleic acid circuitry have led to the creation of waste-free, entropy-driven DNA amplifiers that reduce circuit leakage and improve detection reliability. These systems are increasingly utilized for quantifying low-abundance miRNAs in cellular contexts. For instance, Chen *et al.* designed a smart photoelectrochemical biosensor that integrated a waste-free entropy-driven DNA amplifier with superparamagnetic Fe_3O_4@SiO_2 particle enrichment.[186] This innovative approach allowed for the highly specific detection of miRNA-155 at an impressive LOD of 3.2 aM. This research provided a new perspective for the detection of miRNAs in complex biological systems, facilitated the development of waste-free DNA molecular machines, and advanced the field of DNA-based nanotechnologies.

The detection of multiple biomarkers in complex biological systems provides enhanced reliability compared to single-analyte approaches. In this regard, Xie *et al.* have developed a pioneering electrochemical biosensor equipped with computational capabilities, effectively functioning as an intelligent automaton for logic-based biomarker detection.[187] As illustrated in Fig. 6d, the system employed predefined logical combinations of miRNA-21 and miRNA-122 as detection modes, implementing corresponding AND and OR logical automata. By integrating target recognition, signal processing, and computational analysis, it simplified the detection process, delivering binary results ("0" or "1") based on computational algorithms. The modular design allows adaptation to various biomarker panels, enhancing potential clinical diagnostics and paving the way for next-generation intelligent biosensing platforms.

4.4 Surface plasmon resonance (SPR) sensing strategy

SPR sensors operate based on the phenomenon of collective electron oscillations on the surfaces of noble metals such as gold or silver. When the refractive index at the metal surface changes, the conditions for plasmon resonance are altered, resulting in a shift in the resonance absorption peak or a change in its intensity.[188] The output signal is typically a shift in either wavelength (λ) or angle (θ). The integration of logical gating with SPR can be achieved by functionalizing the gold surface with two distinct aptamers or DNA strands, each tailored to capture specific target molecules. A significant SPR signal shift, indicating a "1" output, occurs only when the target molecules are present in a specific logical combination. Under these conditions, the target molecules work together to form a complete and more rigid composite layer on the sensor surface, inducing a substantial change in the refractive index. Conversely, in the absence of the appropriate logical molecular combination, binding is weak or disordered, resulting in minimal refractive index change and a weak signal output ("0").

AuNPs are extensively utilized in SPR sensors due to their unique plasmonic properties. However, the strong non-specific adsorption of interferents on AuNP surfaces can compromise detection accuracy. To tackle this issue, Zhang *et al.* introduced a dual-signal channel assay for detecting Hg^{2+} ions, employing an AND logic gate that harnesses both the plasmonic and nanozyme characteristics of AuNPs.[189] This strategy utilized the dual response of the AuNP nanoprobes to implement logical operation through an AND gate, effectively distinguishing Hg^{2+} from interfering substances. By introducing an additional decision criterion, this method significantly enhanced the accuracy of Hg^{2+} detection. This dual-channel response strategy demonstrated substantial promise for elevating the performance of AuNP-based SPR sensing platforms.

4.5 Thermosensitive and mass-sensitive sensing strategies

Thermosensitive sensors generally employ polymer thermosensitive materials that exhibit a lower critical solution temperature (LCST). When the temperature is below the LCST, the polymer chains maintain a hydrophilic and extended conformation. However, once the temperature exceeds the LCST, they undergo a hydrophobic collapse, resulting in significant changes in solution turbidity or volume phase transition.[190,191] The output signal is typically characterized by variations in light transmittance or volume. By integrating logic recognition elements, such as enzyme-cleavable peptide linkers or DNA cross-linkers, into thermosensitive materials and fine-tuning the LCST to align with near physiological temperatures, a logic-gated sensing mechanism can be created. A notable change in turbidity or volume ("output 1") occurs only when target molecules are present in a specific logical combination that cooperatively cleaves the cross-linking points within the material, thereby drastically altering its LCST and phase transition behavior at the operating temperature. In the case of a single input, the cross-links remain largely intact, and no pronounced phase transition occurs. For instance, Wu *et al.* introduced a comprehensive logic gate system utilizing the light-responsive sensor material $BiFeO_3$.[192] This sensor could detect not only light intensity and temperature but also perform three fundamental logic operations: AND, OR, and NOT. It successfully detected optical and thermal patterns and accurately produced the corresponding logic outputs. This work provided a new way for constructing highly integrated multifunctional logic devices that can advance large-scale sensing, communication, and computing operations.

Mass or force-sensitive sensors, primarily represented by quartz crystal microbalance or cantilever-based systems, operate on the piezoelectric effect.[193] When there is a change in mass

on the crystal surface, its intrinsic resonant frequency shifts, generating an output signal that manifests as a change in frequency or mass response. Logic-gated mass-sensitive sensing can be achieved by engineering DNA nanostructures or dendritic molecules on the mass-sensitive electrode, designed to require specific logical triggers for assembly. Only when target molecules are present in the precise logical combination do they act as "fuels" to trigger structural reorganization or hybridization reactions. This induces a significant frequency decrease, corresponding to a "1" output. A single input is insufficient to initiate large-scale assembly, thereby enabling logic-gated force-sensitive detection.[194,195] For instance, Cao *et al.* fabricated mechanically responsive ion channels by axially coating CNT fibers with polymers of different elastic moduli. The ion rectification of these channels could be controlled by the differential mechanical response of the CNT fibers to stress.[196] By integrating these channels into logic gate devices, the authors achieved AND and OR logic operations. This conceptual framework provided a simple and cost-effective method for fabricating ion channels, highlighting their potential for use in complex, highly integrated ionic logic circuits.

4.6 Integration with intelligent sensing strategies

Although molecular logic operations hold great promise, they still face challenges such as slow processing speeds, difficulties in signal conversion, and limited programmability and general applicability. To address these issues, researchers have embarked on integrating molecular logic computing with cutting-edge modern intelligent technologies, such as smartphones, AI, and machine learning.[197–199] This integration paves the way for the construction of intelligent sensing and processing systems that bridge the microscopic and macroscopic worlds. As illustrated in Fig. 7, an integrated strategy can be achieved by combining molecular logic sensing (molecular layer), smartphone-based signal conversion (signal conversion layer), and AI-powered cloud computing (AI layer).

Molecular logic systems serve as intelligent front-end sensors. By designing functional molecular logic gates (*e.g.*, AND, OR, XOR) or more complex computational networks, these systems can be engineered to respond specifically to a wide range of environmental stimuli, including specific ions, pH, temperature, disease biomarkers, or toxins.[37,38] These molecular systems are capable of performing preliminary, parallel information processing at the molecular level. For instance, Li *et al.* developed a cell-free logic-gated detection system based on a three-layer polymerase chain reaction architecture.[200] This architecture consisted of a sensing layer, a processing layer, and a signal amplification layer, enabling the detection of target ligands, the conversion of nucleic acid signals, and the generation of an amplified fluorescent output (Fig. 7a). This design significantly enhanced detection sensitivity, achieving limits of 0.025 μM for tetracycline and 0.1 μM for zinc. This system demonstrated broad applicability for signal amplification in cell-free biosensors and provided a generalizable methodology that paved the way for enhanced biosensor performance and expanded detection capabilities.

Smartphones and other physical devices serve as versatile signal converters (or bridges) that transform the results of molecular computations, which are typically optical or electrochemical signals, into digital data. This conversion is achieved using built-in components such as optical cameras, photodiodes, electrochemical sensors, or portable spectrometers. To meet the demand for rapid, portable, and multiplex on-site detection, Li *et al.* proposed an integrated intelligent system.[201] This approach involved optimizing multiplex recombinase polymerase amplification primers to achieve efficient simultaneous amplification of CaMV35S and NOS genes in a single reaction tube, overcoming challenges such as primer interference and low amplification efficiency in multi-target assays. Combined with built-in heating and backlight modules, the device enabled a fully portable workflow that integrated amplification, cleavage, and color development. To eliminate reliance on subjective visual assessment, a deep learning algorithm was implemented for automated object detection and grayscale analysis, allowing results to be automatically recognized *via* a smartphone (Fig. 7b). Furthermore, smartphone-based sensing platforms also allowed for highly sensitive gene detection, such as targeting viral genes, at the point of care applications.[202] Such systems hold great potential for distributed diagnostic testing in primary care settings, particularly in resource-limited regions, and support timely sharing of epidemiological data.

AI computing can serve as a central processor (or "brain"), leveraging its powerful computational capabilities, connectivity, and advanced algorithms to perform in-depth data analysis, storage, visualization, and decision-making. In this respect, Zhao *et al.* developed a machine learning-enabled dual-channel droplet biosensor platform for meat authenticity verification.[203] This system enabled rapid identification and analysis of animal-derived components in food samples. The biosensor employed a CRISPR/Cas12a-mediated fluorescence detection mechanism, which converted and amplified nucleic acid signals into fluorescent outputs. In this assay, a smartphone application was also developed by integrating with a random forest machine learning model to analyze key parameters, including droplet area, fluorescence intensity, and count to ensure precise image capture and processing (Fig. 7c). The proposed biosensor accurately detected ND1 (pig-specific) and IL-2 (duck-specific) genes even in highly processed meat products, demonstrating greater robustness and practicality compared to conventional methods. By integrating smartphone-based microscopic imaging with deep learning, one-click classification could also be achieved. This enabled accelerated model inference, full automation, and on-site testing, offering efficient diagnostic solutions especially suited for resource-limited settings.[197,198]

The integration of molecular logic computation with modern intelligent technologies represents a strategic pathway for building the foundation of a future smart society. It is not merely a combination of existing technologies, but rather the creation of a new, bio-inspired paradigm for information sensing and processing. Although challenges remain, such as improving the stability of molecular systems, standardizing signal readouts, and miniaturizing integrated devices, the

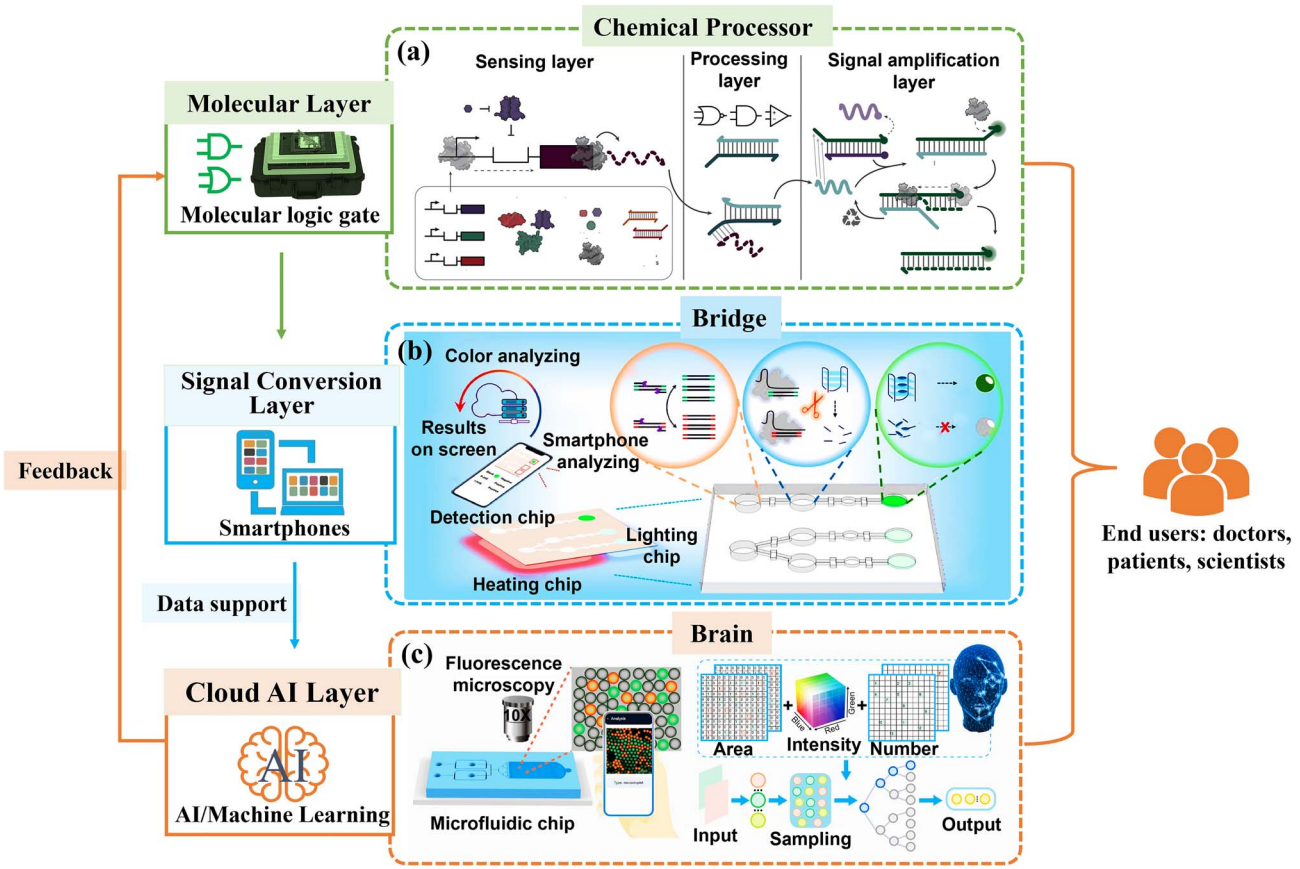


Fig. 7 Integration of molecular logic operations with intelligent sensing strategies. (a) Construction of the cell-free logic-gated sensing and detection system, which comprised a three-layer architecture: a sensing layer, a processing layer, and a signal amplification layer. Reproduced with permission.[200] Copyright 2025, Springer Nature Limited. (b) A portable, smartphone-based detection device developed for on-site analysis and quantitative signal readout. Reproduced with permission.[201] Copyright 2025, Elsevier. (c) Machine learning-assisted dual-channel droplet biosensor platform for meat species authentication. Reproduced with permission.[203] Copyright 2024, the American Chemical Society.

strategic value and application prospects of this convergence are clear. Ultimately, it promises to contribute to a world with sharper sensing, smarter decision-making, and faster response capabilities.

5 Enhanced biosensing applications by using molecular logic computing toolkits

5.1 Enhanced biosensing: comparison with conventional sensing

The evolution of biosensing technologies has followed two distinct paradigms. Conventional sensing strategies operate on a direct-readout model wherein singular molecular recognition events generate measurable signals. In contrast, molecular logic-based sensing constitutes a fundamentally different approach inspired by digital computing principles. By constructing nucleic acids, proteins, and enzymes into computational elements, these systems execute Boolean operations (AND, OR, XOR, INHIBIT). These operations integrate diverse biological inputs such as specific miRNAs, enzymatic activities, pH variations, or small molecules to produce programmed outputs.[34,204] This paradigm shift from specific detection to programmable computation represents the emergence of dynamic, software-defined chemical systems capable of sophisticated information processing at the molecular level. A comparative analysis of molecular logic gate-based sensing *versus* traditional sensing is presented in Table 3, highlighting a fundamental dichotomy between conventional analytical strategies and emerging molecular logic approaches in terms of both performance and operational philosophy.

Conventional sensing methods are primarily designed for the quantification of single analytes, relying on highly specific molecular recognition events to achieve selectivity. Such platforms have achieved robust commercial and clinical adoption, as evidenced by widespread applications including glucose monitors, pregnancy tests, and COVID-19 antigen tests,[205,206] demonstrating successful translation into home and point-of-care settings. For more complex diagnostic needs, established technologies such as qPCR/digital PCR,[207] immunoassays,[208,209] and next-generation sequencing[210,211] remain indispensable gold standards, providing critical capabilities in infectious disease management, cancer genotyping, and non-invasive prenatal testing. Ongoing development efforts are accordingly

Table 3 Comparison of conventional strategies and molecular logic strategies in biosensing

Analysis performance	Conventional strategies	Molecular logic strategies
Core function	Quantification of a single analyte	Boolean computation based on multiple inputs
Number of inputs	Typically one (the target analyte)	Inherently multi-input (2, 3, or more)
Selectivity source	Molecular recognition fidelity (lock-and-key)	Programmable Boolean logic (pattern recognition)
LOD	Excellent	Variable (typically nanomolar range)
Robustness	High (decades of optimization)	Moderate (platform-dependent)
Programmability	None (fixed detection parameters)	Exceptional (inherent capability)
Scalability	Limited (physical multiplexing constraints)	High (theoretical multiplexing superiority)
Output signal	Analog, continuous, proportional to concentration	Digital-like, binary (ON/OFF, yes/no)
Modularity & programmability	Low; a new sensor must be designed for each new task	High; same platform can be reconfigured for different logic
Information density	Low (one piece of data per sensor)	High (one sensor delivers a complex diagnostic result)
Integration with computing	Output must be processed by an external device	The molecule itself serves as the computational unit

focused on enhancing automation and reducing costs to improve the accessibility of these tools. However, conventional strategies suffer from inherent limitations. These systems typically operate as single-input devices, lacking programmability due to their fixed detection parameters. Furthermore, their scalability is hampered by physical multiplexing constraints, which restrict simultaneous multi-analyte detection. The output signal is generally analog and continuous, correlating directly with analyte concentration. Consequently, this design yields low information density, with each sensor generating only a single data point. As a result, substantial external computation is often required for signal processing and interpretation, limiting their adaptability for complex diagnostic scenarios.

In contrast, molecular logic strategies are characterized by their capacity to perform Boolean computations using multiple inputs. Selectivity in these systems arises from programmable logical operations enabling advanced pattern recognition. Although current implementations often exhibit variable detection limits (typically in the nanomolar range) and moderate, platform-dependent robustness, they offer inherent programmability and exceptional theoretical scalability. A key advantage lies in their modularity; the same molecular platform can be reconfigured for different logical tasks without fundamental redesign. These systems produce digital-like, binary outputs (0/1) that boost information density, allowing a single molecular sensor to deliver complex diagnostics based on multiple inputs. Most notably, computation is embedded within the molecular system itself, effectively allowing the molecule to serve as the computer and integrating sensing and logical processing at the point of measurement.

Despite the fact that most molecular logic configurations remain at the proof-of-concept stage-with only elementary logic gates such as AND gates approaching practical application, several promising translational pathways have recently emerged. These include *in vivo* diagnostic and therapeutic systems, multiplexed pathogen discrimination, and intelligent biomarker interpretation.

Among these, *in vivo* diagnostic and therapeutic applications utilizing DNA/RNA-based logic circuits represent one of the most compelling approaches. For instance, AND-gated DNA nanodevices designed to release therapeutic agents only upon simultaneous detection of two cancer-specific antigens have demonstrated significantly improved safety profiles in animal models by substantially reducing off-target effects.[212] Other advances include logic-gated DNA nanostructures that enable spatially controlled ATP and glutathione imaging within mitochondria using AND-gate operation, markedly improving tumor-to-normal tissue contrast.[213]

Multiplexed pathogen discrimination through molecular computational methods allows for differential diagnosis within a single reaction vessel. By employing logical operations that produce pathogen-specific fluorescent barcodes, these systems can effectively distinguish between related respiratory viruses-such as influenza and SARS-CoV-2-with a theoretical multiplexing efficiency surpassing that of conventional physical multiplexing approaches.[214] For example, Lim *et al.* developed a logic-gated, amplification-free CRISPR-Cascade detection system[215] that incorporated a positive feedback loop, enabling detection of pathogen DNA without nucleic acid amplification within 10 minutes at a signal-to-noise ratio > 1.3. In another study, Weng *et al.* constructed a versatile logic-gated DNAzyme-amplified protease sensing platform by integrating cationic peptides with DNAzymes,[216] enabling rapid detection of various proteases. Compared to conventional non-amplified protease sensors, this platform exhibited significantly improved sensitivity, allowing for accurate SARS-CoV-2 diagnosis and reliable classification of colorectal cancer.

Intelligent biomarker interpretation represents a paradigm shift from mere concentration measurement toward evaluating clinically meaningful relationships among multiple analytes. By implementing a conditional logic statement, these systems can achieve more accurate prostate cancer risk stratification than single-analyte quantification. Illustrative examples include miRNA-responsive AND-logic-gated RNA devices for precision diagnostics and therapeutics[217] as well as logic-gated biosensors

that integrate an additional layer of information processing between sensing and output to synthesize complex diagnostic conclusions.[204]

5.2 Biosensing applications

5.2.1 Genetic analysis. In the rapidly advancing fields of precision medicine and molecular diagnostics, genetic analysis has become a core tool for revealing the code of life and enabling early disease detection.[218] A crucial factor propelling advancements in this field is the accurate identification and dynamic monitoring of nucleic acids-the essential carriers of genetic information. Beyond their critical role in gene expression, nucleic acids are gaining recognition as highly promising targets in biosensing technologies. Abnormal expression patterns and mutations in nucleic acids are strongly linked to various diseases, making their detection crucial for disease screening and risk assessment.[219] To improve detection sensitivity and efficiency, researchers have integrated intelligent molecular logic computation into biomolecular sensing.[73,75] This innovative approach combines the selective recognition of targets by functional nucleic acids with advanced signal amplification strategies, leading to the development of highly accurate and efficient diagnostic systems.

In genetic analysis, the primary research focus lies in DNA and RNA analysis studies. The integration of logic gating facilitates rapid and intelligent signal switching and amplification for genetic analysis. Bonnet *et al.* developed a three-terminal device known as a transcriptor, which employed phage serine integrase to regulate the flow of RNA polymerase along DNA.[15] This innovative approach enabled the permanent amplification of logic gates (AND, OR, NOR, XOR, NAND, and XNOR) triggered by standard control signals, as well as sequence-based logic that promoted autonomous intercellular communication through DNA-encoded logic states. The single-layer digital logic architecture introduced here allowed for the engineering of amplified logic gates that could precisely modulate transcription rates both within and across different organisms.

The programmability of DNA-based molecular logic devices enables the design of dynamic, sequential DNA circuits capable of spatially organizing different DNA species. Emanuelson *et al.* developed an activated fluorescent reporter utilizing a DNA strand displacement circuit.[220] Upon specific DNA input, a sequential strand displacement reaction was triggered, facilitated by the hybridization between a probe-mediated vinyl-ether-caged fluorophore and its complementary tetrazine partner, resulting in fluorescence activation. Unlike traditional fluorophore-quencher systems, this approach offered a key advantage for DNA computing in mammalian cells (Fig. 8a). Fluorescence activation was independent of circuit degradation, eliminating false signals. The reporter's robustness and sensitivity were validated by its successful application as a readout device for DNA logic circuits in live cells.

For RNA analysis, the DNA molecular logic tools were mostly used for the analysis of miRNAs. As shown in Fig. 8b, Wen *et al.* developed an innovative biosensing platform for the highly specific and sensitive detection of bi-mature miRNAs.[221] This platform functioned as a second-order logic biosensor, merging the YES logic gate capability of DNA nanocages with the AND logic gate functionality of CRISPR/Cas12a. The DNA nanocages allowed for selective differentiation between mature miRNAs and pre-miRNAs, thus expanding potential applications in biological science research and clinical disease diagnosis.

In addition, molecular logic gates offer an intelligent solution for the simultaneous detection of multiple biomarkers. Shi *et al.* developed a dual-mode DNA logic gate system for POCT, enabling portable and intelligent detection of various miRNAs.[222] In this system, platinum-coated gold nanoparticles (Au@PtNPs) with catalase-like activity served as signal reporters. The presence of target miRNAs triggered a strand displacement reaction, leading to a substantial accumulation of Au@PtNPs. This accumulation permitted the visual detection of miRNAs through lateral flow strip analysis. As shown in Fig. 8c, this strategy effectively implemented two-input and three-input AND logic gates, facilitating multiplex detection of two and three miRNAs, respectively. This approach presents a promising platform for advanced multi-input biomarker analysis, paving the way for the development of intelligent and portable biosensing and bioanalytical systems.

5.2.2 Cancer analysis. Detection of cancer-related biomarkers is extremely important for cancer screening and early anti-tumour therapy. Logic-gated biosensors utilize logic-based bio-computation to rapidly and accurately generate detection results upon receiving input signals, simplifying the complex detection process. Moreover, logic-gated operation in response to multiple signals simultaneously can be realized, which in turn enhances precise disease targeting.

Tumor-associated antigens are not exclusively expressed in cancer cells, and the complex tumor microenvironment renders single-stimulus responses inadequate.[223] Thus, developing reliable methods for precise cancer cell eradication is a major research focus.[224] To facilitate the precise identification of cancer cells, well-crafted molecular logic circuits can be employed to achieve intelligent discrimination of cancer targets.[217,225] As shown in Fig. 8d, Sima *et al.* developed a straightforward and effective DNA-based logic circuit that could accurately identify cancer cells while exhibiting outstanding performance in tumor imaging.[226] This promoted the use of DNA logic circuits in advancing convenient and intelligent precision diagnostics. Chao *et al.* developed an innovative computational system that integrated a logic gate for computation and release, a dual-amplification DNA cascade circuit, and an MnO_2 nanocarrier.[227] The system was specifically designed to logically process the expression levels of miRNA-21 and miRNA-892b in cells, generating fluorescent signals based on their relative concentrations (Fig. 8e). By simultaneously detecting these two biomarkers, it facilitated the accurate identification of cancer cells, even within heterogeneous cell populations.

In addition, logic-gated tumor microenvironmental nanoamplifiers that utilized logical gating to facilitate targeted delivery of CRISPR/Cas9 for multimodal cancer therapy have been studied. Pan *et al.* developed a system that encapsulated the CRISPR-associated 9 protein and glucose oxidase (GO_x)

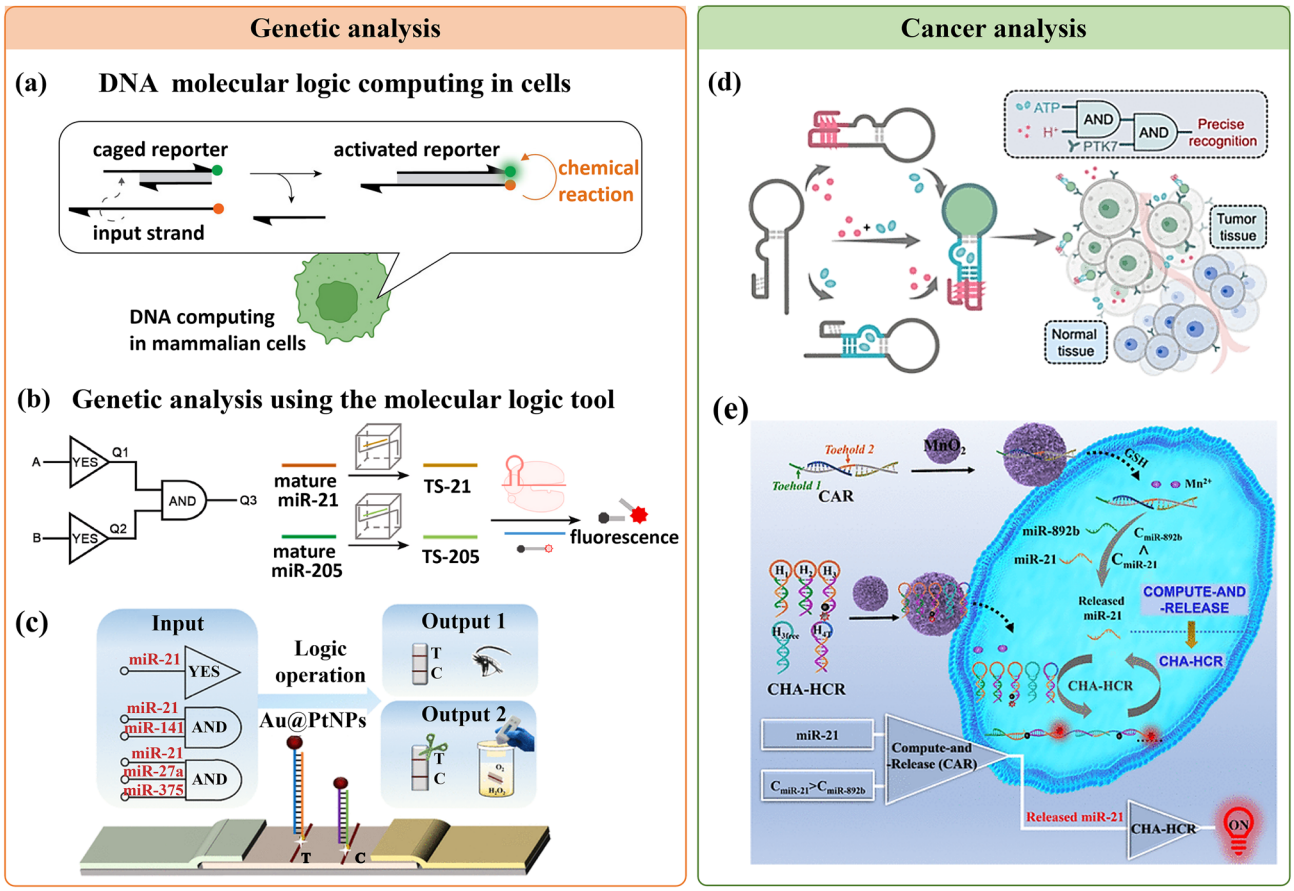


Fig. 8 Genetic analysis and cancer analysis by using molecular logic computing toolkits. (a) Schematic of a DNA logic intracellular small molecule activation circuit. Reproduced with permission.[220] Copyright 2024, American Chemical Society. (b) Schematic of a logic biosensor platform based on CRISPR/Cas12a and DNA nanocages for miRNA analysis. Reproduced with permission.[221] Copyright 2024, Elsevier. (c) Schematic of a dual-mode molecular logic for intelligent portable miRNA detection. Reproduced with permission.[222] Copyright 2023, American Chemical Society. (d) Schematic of DNA molecular logic circuit for accurate tumor identification. Reproduced with permission.[226] Copyright 2024, American Chemical Society. (e) Schematic of the compute-and-release logic-gated DNA cascade circuit for accurate cancer analysis. Reproduced with permission.[227] Copyright 2023, the American Chemical Society.

within an amorphous zeolite imidazolium ester skeleton-8 (CG@ZIF-8).[228] This CG@ZIF-8 construct was subsequently coated with a covalent-organic framework (COF) that degraded under anoxic conditions and loaded with DNAenzymes capable of cleaving peroxidase mRNAs, resulting in an acid "AND" hypoxia logic-gated gene editing platform. This self-amplifying gene-editing strategy incorporated an AND logic gate responsive to pathological markers (acidosis and hypoxia), enhancing therapeutic precision while reducing genotoxicity. This approach highlights the potential of biocomputing-based CRISPR delivery systems in targeted cancer therapy.

Integrating Boolean logic into CAR T cells is essential for enabling them to differentiate between healthy and cancerous tissues, a critical requirement for effectively targeting a wide range of solid tumors.[229] In this vein, Tousley *et al.* developed a logic-gated intracellular network that operated *via* the LAT-SLP-76 signaling scaffold.[230] This innovative system marked the engineered CAR T-cell platform that restricted T-cell activation to interactions with dual antigens in a direct, transient, and reversible manner.

By employing logic gates as a framework, researchers can improve cancer selectivity and therapeutic efficacy in solid tumors through the implementation of dual-input systems, such as dual-specific CAR-T cells or multi-specific T cell engagers, rather than relying solely on single-input approaches.[231,232] In addition to traditional dual-antigen targeting utilizing OR-gate and AND-gate logic, further tumor-selective inputs-including pH levels, hypoxia, antigen density, tumor protease activity, and gradients of immunosuppressive cytokines-can be creatively integrated into therapeutic designs. This logic-based approach significantly enhances the precision of cancer detection and treatment, maximizing tumor specificity while minimizing off-target toxicity.

5.2.3 Identification of pathogens. The 2019 COVID-19 pandemic caused by SARS-CoV-2 posed a great threat and burden to global public health. SARS-CoV-2 comprises four main structural proteins (spike (S), nucleocapsid (N), envelope (E), and membrane (M)) and their corresponding genes.[233] The primary method for diagnosing COVID-19 is nucleic acid-based testing, exemplified by quantitative reverse transcription-

polymerase chain reaction (qRT-PCR), which detects the open reading frame 1ab (ORF1ab) and nucleoprotein genes of SARS-CoV-2.[234,235] However, current qRT-PCR techniques are susceptible to false-positive results due to issues such as cross-contamination or nonspecific amplification.[236,237] Fortunately, researchers have leveraged the powerful information processing capabilities and molecular data biocomputing functions of DNA molecular logic gates to tackle these challenges. This innovation has facilitated intelligent screening of multiple SARS-CoV-2 variants, enabled home-based disease surveillance, and reduced the incidence of false-positive misdiagnoses through the development of DNA molecular biocomputing systems.

To address the issue of false-positive misdiagnosis arising from cross-contamination or nonspecific amplification, Chen *et al.* proposed an advanced SARS-CoV-2 RNA detection system that utilized a logic-gated dumbbell-type triple-state molecular switch (DTMS).[237] The DTMS consisted of a triple-helix stem region and two loop regions to detect SARS-CoV-2. The coexistence of ORF1ab and nucleoprotein genes induced a structural rearrangement of the DTMS, shifting two pyrene moieties to the spacer region and producing a unique signal output. This amplification-free method achieved an LOD of 1.3 nM, highlighting its significant potential as a diagnostic tool for COVID-19 and possibly other epidemic surveillance applications.

Multiplexed target detection utilizing logic-gated signal readouts can significantly enhance diagnostic accuracy by minimizing both false-negative and false-positive results. Bhadra *et al.* advanced loop-mediated isothermal amplification (LAMP) assays by integrating oligonucleotide strand exchange probes, which facilitate fluorescent or colorimetric detection through lateral flow test strips.[238] This streamlined one-pot approach maintained operational simplicity while providing accurate sequence-specific verification, allowing for multiplexed amplicon interrogation (for target redundancy or co-detection) and binary (YES/NO) visual readouts.

The emergence of multiple variants of SARS-CoV-2 has markedly increased viral transmissibility and reduced the efficacy of detection.[239] In response to this challenge, Deng *et al.* developed a cutting-edge molecular computing system designed for the intelligent detection of SARS-CoV-2 multiple variants.[240] As shown in Fig. 9a, the system featured six interconnected sequence-specific molecular switches that carried out parallel arithmetic operations, allowing for the simultaneous multi-channel detection of SARS-CoV-2 and its variants. This method facilitated rapid logic-based identification in just 10 min, making it especially advantageous for large-scale variant screening initiatives.

In order to accurately identify infectious individuals with active virus, researchers have investigated methods for detecting active viral particles, in addition to developing sensitive, rapid, and cost-effective techniques for identifying viral fragments. Huang *et al.* introduced an AND logic circuit microfluidic strategy designed to enrich intact SARS-CoV-2 virus.[241] As shown in Fig. 9b, this approach employed a microfluidic enrichment technique based on stoichiometric balanced DNA computation, achieving an LOD of as low as 37 active virus particles per microliter.

In addition to detecting SARS-CoV-2, the molecular logic operation toolkit has also played a critical role in differentiating various viruses in recent years. Li *et al.* developed a dual hairpin ligation-induced temperature amplification protocol that could reliably enable ultrasensitive genotyping, producing a strong fluorescent signal.[242] This method has been successfully utilized for the detection of influenza A, influenza B, MERS-CoV, and SARS-CoV-2 (Fig. 9c). Current diagnostic methods for SARS-CoV-2 and influenza B face significant limitations in home-based disease surveillance due to their dependence on specialized equipment, operational complexity, and the necessity for human intervention. To overcome these challenges, Chen *et al.* designed a highly sensitive time-resolved cascade logic gate microfluidic chip (TCLMC) to achieve one-step, capillary force-driven home self-screening.[243] By integrating logic gates inspired by analog circuits, the TCLMC autonomously managed flow rates and regulated incubation times to optimize the performance of immunoassays. This innovation has considerable potential to enhance early disease detection and reduce transmission rates. In addition, Sen *et al.* developed an electrochemical sensing platform based on trimeric aptamers in conjunction with machine learning algorithms to achieve highly sensitive and specific detection of SARS-CoV-2 and influenza A viruses (H3N2 subtype).[244] The technology effectively integrated the multivalent aptamer enrichment with real-time kinetic monitoring of single-frequency impedance spectroscopy, addressing matrix interference in heterogeneous samples by analyzing 9-dimensional electrochemical features through machine learning.

Moreover, molecular logic-based tools offer the capability for the simultaneous detection of multiple pathogens.[215,245] Petronella *et al.* developed a logic-OR gate plasmonic array that could independently or concurrently identify various bacterial strains, highlighting the system's multiplexing potential.[246] The approach utilized the high sensitivity of colloidal AuNRs to localized refractive index changes, along with their photothermal conversion efficiency, to formulate an optimized AuNR array (Fig. 9d). The platform exhibited exceptional morphological and optical properties for real-time pathogen detection, including *Escherichia coli* and *Streptococcus thermophilus*, as well as enabling on-demand water disinfection. Such versatility is crucial for improving point-of-use water quality monitoring systems.

5.2.4 Living cell logic analysis. The advancement of molecular logic devices with multiple biological computational capabilities offers considerable promise for various life science applications, including cell imaging, cell recognition, and response to cell-specific markers.[247–250] There are two main strategies for conducting molecular logic operations in living cells. The first involves surface-based intelligent cell identification, which relies on membrane-associated protein biomarkers for recognizing cells. The second strategy is intracellular molecular logic analysis, which utilizes internal biomarkers to facilitate multiplexed detection and logic-based responses within the cell. These methods enhance the potential for programmable biological sensing and precision diagnostics.

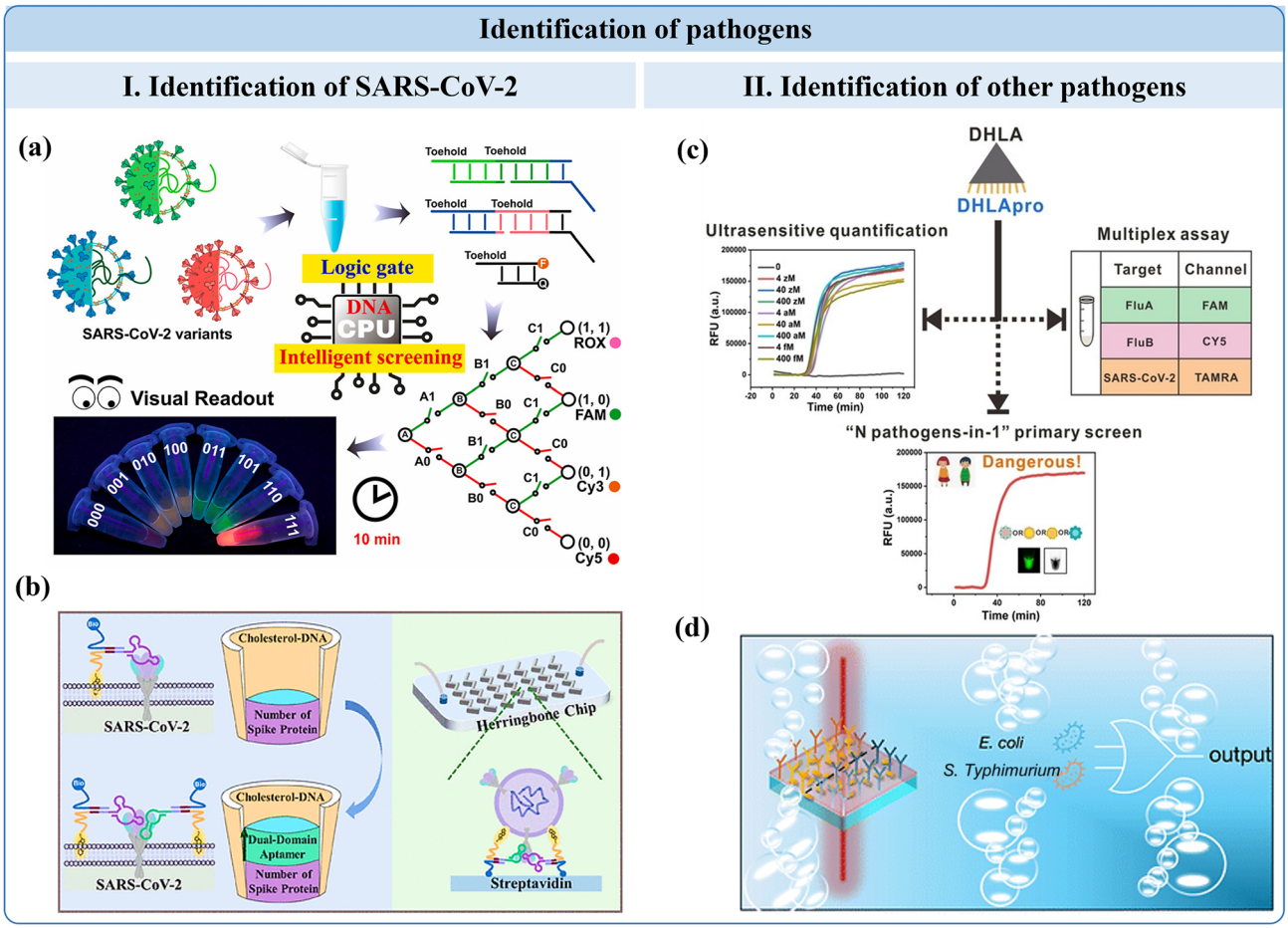


Fig. 9 Identification of pathogens by using molecular logic computing toolkits. (a) Schematic of programmable DNA biocomputing circuits for screening of SARS-CoV-2 variants. Reproduced with permission.[240] Copyright 2022, Elsevier. (b) Schematic of a logical stoichiometric balanced DNA computation strategy for high sensitivity detection of pseudotyped SARS-CoV-2. Reproduced with permission.[241] Copyright 2023, the American Chemical Society. (c) Schematic of a ready-to-use and multimodal logic sensing strategy for detection of multiplex pathogens. Reproduced with permission.[242] Copyright 2022, John Wiley and Sons Ltd. (d) Schematic of a logic-OR gate gold nanorod-based plasmonic biosensor for multipathogen detection. Reproduced with permission.[246] Copyright 2025, the Royal Society of Chemistry.

For cell surface-based intelligent logic analysis, Gong *et al.* developed a cell-membrane-anchored DNA molecular logic system governed by a "YES-AND" logic circuit.[251] The concentrations of extracellular potassium ions (K^+) and ATP exhibited significant variation across different cellular microenvironments, rendering them effective biomarkers for early disease detection and cellular localization. This innovative system combined a bimolecular G-quadruplex with an ATP aptamer, which was anchored to the cell membrane through cholesterol molecules (Fig. 10a). The resulting structure facilitated *in situ* visualization and sensing of the tumor cell microenvironment. Dong *et al.* developed a DNA walker-driven SERS logic aptasensor designed for the highly sensitive and specific identification of tumor cells by enabling membrane protein imaging on individual living cells.[252] The sensor consisted of logic probes, network probes, and EpCAM probes, all of which were anchored on AUNPs. Upon the binding of EpCAM, the DNA walker initiated the assembly of AuNP network nanostructures on the cell membrane, thus allowing the system to execute AND-gated Boolean logic analysis. To achieve more precise molecular logic operations on cell membranes, Fang *et al.* developed a logic-identification cell membrane-guided DNA computing system designed to selectively protect lysosome-targeting chimeras (LYTACs) within cells.[253] As shown in Fig. 10b, this system employed a dsDNA structure that shielded the regions corresponding to the protein of interest and the lysosome-targeting receptor, thereby minimizing systemic toxicity during administration. For experimental validation, the researchers utilized MCF-7 (cancer cells) and MCF-10A (normal cells) as model cell lines. The above approaches facilitate precise detection and classification of cell subtypes, showcasing significant potential for application in precision diagnosis and detection.

For the intracellular molecular logic analysis, while nucleic acid computing has emerged as a revolutionary approach for molecular information processing in chemical and biological environments, implementing molecular logic circuits within cells remains challenging due to the complexity of intracellular conditions. To address this challenge, Sun *et al.* introduced allosteric strand exchange (ASE) as a mechanism to expand

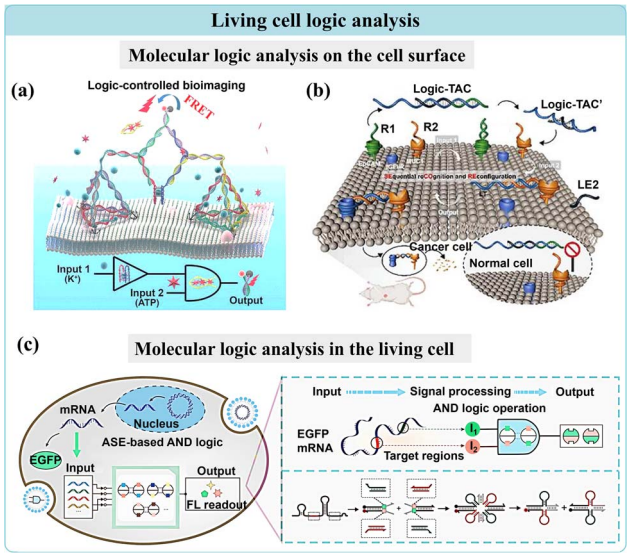


Fig. 10 Living cell logic analysis by using molecular logic computing toolkits. (a) Schematic of the cell-membrane-anchored DNA logic-gated nanoassemblies for extracellular bioimaging. Reproduced with permission.[251] Copyright 2022, the American Chemical Society. (b) Schematic of a logic-identification cell membrane-guided DNA computing system for selectively protecting LYTACs. Reproduced with permission.[253] Copyright 2024, John Wiley and Sons Ltd. (c) Schematic of the implementation of complex nucleic acid circuits in living cells. Reproduced with permission.[254] Copyright 2025, American Association for the Advancement of Science.

nucleic acid-based logic computation in mammalian cells.[254] Their research led to the development of a scalable nucleic acid circuit architecture capable of executing complex Boolean logic functions within a single circuit layer, including AND, OR, AND–OR combinations, and even multi-input expressions with 4 or 8 inputs (Fig. 10c). Notably, these ASE-based circuits can be easily reprogrammed to interface with CRISPR-Cas9 systems, enabling controllable gene editing and demonstrating significant potential for advancing intracellular biocomputing applications.

The integration of gold nanomaterials with molecular logic devices presents remarkable opportunities for enhancing biological research. Building on this idea, Li *et al.* developed a modular DNA logic gate nanomachine that utilized DNAzyme and G-quadruplex-locked gold nanocages (AuNCs).[255] The system contained four mutually corroborating binary logic gates (OR, NOR, XNOR, AND) with miRNA-21 and miRNA-155 as logical inputs, producing Adriamycin fluorescence as outputs and triggering specific responses based on distinct combinations of inputs. Through this tandem logic circuit, the platform facilitated initial screening, precise differentiation, and comprehensive treatment of diseased cells. Wang *et al.* engineered an endogenous enzyme-activated DNA nanomachine that employed AuNCs as a carrier for the simultaneous detection of miRNA-21 and miRNA-210 in living cells.[256] This design utilized cancer-overexpressed enzymes APE1 and telomerase as control switches for the logic circuit, incorporating a signal amplification strategy to achieve highly sensitive *in situ* analysis of intracellular miRNAs. This approach allowed for customizable inputs and outputs, potentially universalizing biosensing applications.

5.2.5 Point-of-care diagnostics and dynamic *in vivo* environmental sensing. In recent years, molecular logic operations have found extensive applications in point-of-care diagnostics and dynamic *in vivo* monitoring. Their programmability, high specificity, and parallel processing capabilities enable complex biomolecular information processing while significantly enhancing the specificity and robustness of biosensing platforms.[185,257]

For point-of-care diagnostics, portable logic-gated sensors, such as paper-based test strips, enable the simultaneous detection of multiple biomarkers. Zhang *et al.* developed an innovative biocomputing platform that integrated personal glucose meters with logic capabilities (Fig. 11a), utilizing metal-specific DNAzymes and natural enzymes as foundational components for detecting various biomolecules in clinical settings.[258] This platform employed DNAzymes and protein enzymes as logical components, demonstrating a versatile system capable of implementing various logic gate responses (YES, NOT, INHIBIT, NOR, NAND, and OR) to diverse biological species. This breakthrough paved the way for the development of intelligent point-of-care devices featuring biomolecular logic gates for field applications. Yang *et al.* reported a split-type electrochemical DNA sensor that integrated a double-stranded LCR with OR logic gates (Fig. 11b).[185] The approach featured several advantages, including low cost, ease of miniaturization, and scalability. These characteristics represent the method's significant potential for point-of-care clinical applications in early diagnosis and monitoring.

The inherent programmability and modifiability of nucleic acids have facilitated the diversification and intelligent advancement of smart molecular logic computation in point-of-care diagnostics for nucleic acid detection. For instance, Yu *et al.* developed a dual-mode fluorescence and photothermal logic sensing platform for the detection of miRNA.[257] This system incorporated CeO_2@Au nanozymes into an AND logic circuit, wherein the presence of two specific miRNA inputs activated a photothermal signal output. This dual-mode logic biosensor could be easily customized for various nucleic acid biomarkers and other point-of-care signal readout methods by simply adjusting the recognition sequences and modification strategies. This flexibility opens up possibilities for developing intelligent and adaptable diagnostics in point-of-care testing.

For dynamic *in vivo* environment sensing, implantable nanomachines offer the potential for continuous, logic-guided monitoring of metabolites such as glucose and lactate, providing real-time feedback to external devices. A recent advancement by Tu *et al.* demonstrated this concept through the development of a dual-activated DNAzyme sensor spatially confined within a DNA nanocage cavity for logic-gated molecular imaging (Fig. 11c).[259] While traditional DNA-based molecular logic tools for live-cell detection and imaging encounter challenges related to limited spatial control and poor biostability, the reported engineered system accomplished controlled spatial confinement of carefully designed, miRNA-

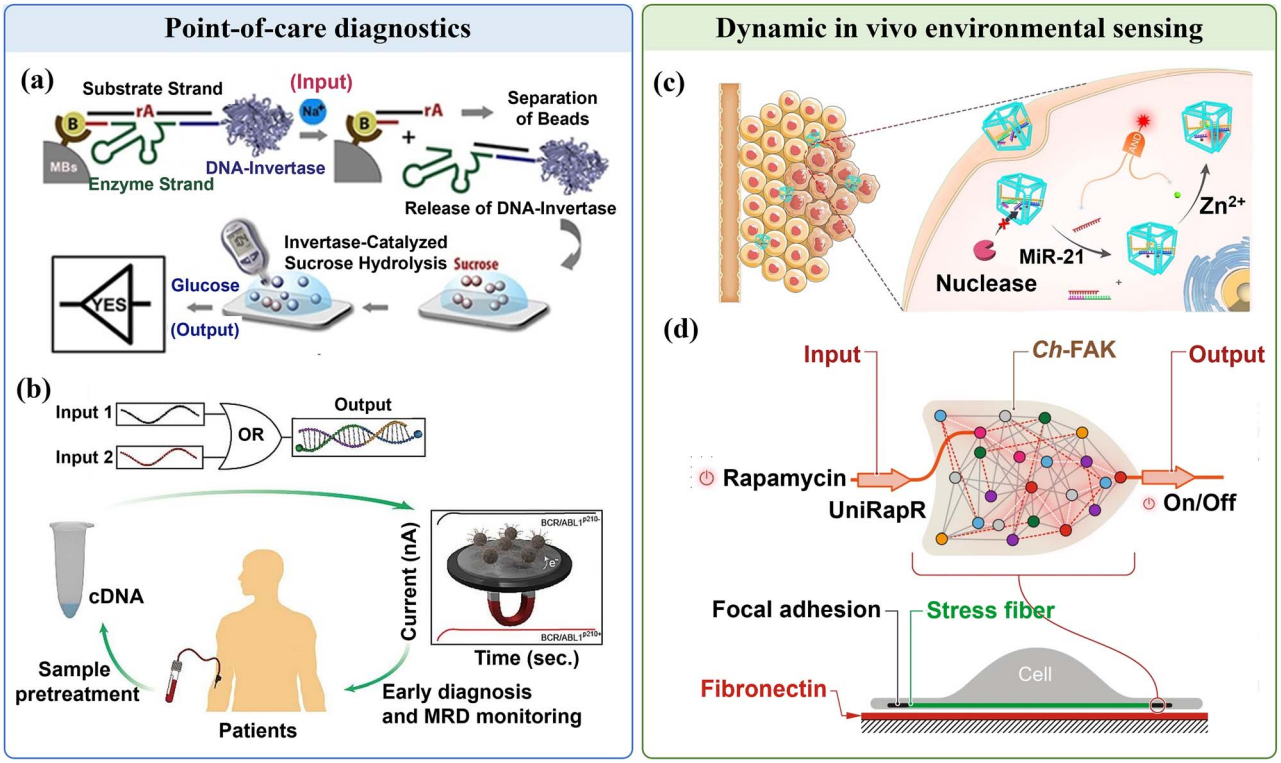


Fig. 11 Application of DNA logical circuits in point-of-care diagnostics and dynamic *in vivo* environmental sensing. (a) Schematic of a logic-gate responsive device for portable and quantitative point-of-care diagnostics. Reproduced with permission.[258] Copyright 2018, John Wiley and Sons Ltd. (b) Schematic of a split-type electrochemical DNA sensor for point-of-care testing of clinical samples. Reproduced with permission.[185] Copyright 2023, Elsevier. (c) Schematic of a dual-activatable DNAzyme sensor for logic-gated intracellular target sensing. Reproduced with permission.[259] Copyright 2025, John Wiley and Sons Ltd. (d) Schematic of a two-input protein logic gate for computation in living cells. Reproduced with permission.[166] Copyright 2021, Springer Nature.

activatable DNAzyme probes within the nanocage. This innovative design not only allowed for efficient intracellular delivery but also enhanced biostability for AND-gate molecular imaging, establishing a platform for self-delivering and self-protecting activatable DNA nanosensor devices capable of detecting a wide range of intracellular targets.

Beyond molecular detection, understanding cellular dynamics in complex microenvironments remains challenging, particularly regarding the correlation and causality between focal adhesion kinase activity and cellular structural complexity. Addressing this, Vishweshwaraiah *et al.* developed a two-input protein-based logic gate for live-cell computation (Fig. 11d),[166] where allosterically engineered orthogonal switches propagated signals *via* independent pathways to execute logical operations at target sites.

These advancements open new possibilities for investigating *in vivo* environments, with potential applications that include real-time monitoring and modulation of biological systems, disease diagnosis, targeted drug delivery, and the rewiring of cell signaling pathways. Furthermore, they facilitate context-aware sensing of metals, pH levels, and temperature. Such programmable nano-computing agents can usher in a new era of robust and complex biomedical and biotechnological applications, ranging from precision therapeutics to synthetic biology.

In addition to the above applications, molecular logic computing has also demonstrated significant potential in addressing core challenges in practical applications, particularly in clinical diagnostics. Moreover, by integration of modern intelligent technologies, such as smartphones,[125,185] AI,[186] and machine learning,[162,187,188] molecular logic toolkits have dramatically broadened the scope across diverse disciplines, highlighting their strong potential for future innovation. This molecular logic technology greatly simplifies the processing of complex sensing information while advancing intelligent data computation and processing capabilities. As summarized in Table 4, the various types of molecular logic computations, sensing targets, sensing strategies, logic functionalities, and applications are outlined. Molecular logic toolkits have opened up considerable opportunities in diverse fields, ranging from medical diagnostics to food safety.

The future translational potential of molecular logic is dependent not on computational complexity, but rather on its capacity to deliver efficient, reliable, and cost-effective solutions to clearly defined problems. The most promising strategies are logic operations as tools for functional integration and intelligent response. In essence, the route to commercialization involves simplifying complexity and enhancing practicality. Translational strategies are generally application-driven, exemplified by logic-gate-based multiplexed biosensing for

Table 4 A list of the applications of intelligent molecular logic computing toolkits in biosensing

Logic computation type	Target	Sensing strategy	Functionality	Application	LOD	Linear range	Ref.
Boolean logic	Sgc8c TCO_1 Sgc4f	Fluorescence	Modular multi-signal integration	Cancer analysis living cell logic analysis	—	—	84
Sequential logic and combinatorial logic	Aflatoxin B1 and ochratoxin A	Fluorescence	Data latche	Environmental monitoring	—	—	55
Fuzzy logic	G-quadruplex DNA, $HO\cdot$, and Fe^{2+}	Fluorescence	Activatable OFF–ON control	Environmental monitoring	2.0 nM (G-quadruplex DNA)	16–338 nM (G-quadruplex DNA)	62
Boolean logic	APE1 miRNA-224	Fluorescence	Activatable lock–key reconfigurable control	Cancer analysis	0.04 U mL^{-1} (APE1) 760 fM (miRNA-224)	0.05–50 U mL^{-1} (APE1) 0.002–20 nM (miRNA-224)	140
Advanced feedback systems and combinatorial logic	miRNA-21 and miRNA-155	Fluorescence	Programmable control	Cancer analysis	1 pM	—	59
Advanced feedback systems	Hepatitis B virus Bladder cancer	Fluorescence	—	Genetic analysis	5.0 aM	—	57
Reversible logic Combinatorial logic	—	Fluorescence	Programmable control reusability	Proof of concept	—	—	40
Sequential logic	—	Fluorescence	Modular multi-signal integration	Proof of concept	—	—	54
Combinatorial logic	miRNA-122 miRNA-221 miRNA-222	Fluorescence	Modular multi-signal integration	Genetic analysis, living cell logic analysis	0.078 nM (miRNA-122) 0.011 nM (miRNA-221) 0.011 nM (miRNA-222)	—	135
Boolean logic	miRNA-21	Photoluminescence	Programmable control	Genetic analysis	4.5 pM	10 pM to 50 nM	128
Boolean logic	HGF TNF-α	Fluorescence	Activatable lock–key reconfigurable control	Living cell logic analysis	—	—	143
Boolean logic	TNF-α IFN-γ	SERS	Programmable control	Cancer analysis	0.2 ng mL^{-1} (TNF-α) 14.6 pg mL^{-1} (IFN-γ)	—	150
Boolean logic	c-Met and CD71	FRET	Programmable control	Living cell logic analysis	—	—	147
Combinatorial logic	miRNA-21 miRNA-20a miRNA-106a	Electrochemical	Modular multi-signal integration	Genetic analysis	10^{-17} M	10^{-16}–10^{-13} M	104
Boolean logic	Tetracycline $ZnSO_4$	Fluorescence	Programmable control	Proof of concept	—	—	102
Combinatorial logic	SARS-CoV-2 variant	Fluorescence colorimetric	Modular multi-signal integration	Pathogen identification	1 nM	—	240

integrated diagnostics,[260,261] stimulus-responsive systems for targeted therapy,[262,263] and functional modules for synthetic biology circuits.[264,265] In contrast, proof-of-concept strategies often remain focused on technology rather than practical applications, emphasizing computational power rather than solving real-world issues. These approaches face significant challenges, including large-scale networks plagued by signal attenuation and noise, and impractical molecular systems aiming for universal computation, which ignore the inherent limitations of molecular substrates. Consequently, the future of molecular logic does not lie in supplanting computers, but in equipping molecules and cells with "intelligent switches". This shift requires moving away from complexity and towards the development of "good-enough" systems that can integrate with established platforms in materials science, microfluidics, and drug delivery, ultimately creating intelligent biotechnologies that address real-world needs.

5.3 Critical challenges and limitations

5.3.1 Cost and economic viability. The elevated cost of molecular logic systems is not solely a manufacturing issue but is intrinsically linked to the materials and processes involved. The development of functional components such as DNA/RNA strands (*e.g.*, aptamers, DNAzymes), proteins, and other molecular elements requires *de novo* synthesis and extensive screening, such as the SELEX technology for aptamer selection,[266] which is both time-intensive and costly. Additionally, many of these systems rely on costly fluorophores (like cyanine dyes) or quenchers for optical signal detection, while electrochemical platforms often require specialized electrodes modified with precious metals, such as gold.[267] The need for high-purity oligonucleotides and organic compounds further escalates expenses, particularly when scaling up to larger production levels. Such economic barriers hinder the transition from academic proof-of-concept to commercial viability, severely limiting broader accessibility and adoption, especially in applications like environmental monitoring. Thus, going forward, more economical and practical strategies need to be developed to meet the application requirements of nucleic acid molecular logic gating.

5.3.2 Operational complexity and practical usability. A significant barrier to the real-world deployment of molecular logic systems is the gap between controlled laboratory environments and practical application settings. Sample preparation often requires stringent conditions, including specific buffer compositions, precise ion concentrations (such as Mg^{2+} for DNAzymes),[268] the removal of inhibitors, and accurate pH control. These requirements can adversely impact the feasibility of simple and rapid analyses. While molecular logic systems can generate straightforward binary outputs, the necessary instrumentation for signal generation and interpretation, such as thermal cyclers, flow cytometers, or confocal microscopes,[269] remain relatively complex and ill-suited for point-of-care or field applications. Furthermore, cascading multiple logic gates, which is essential for advanced computations, leads to challenges such as signal cross-talk between components, progressive signal degradation, and kinetic mismatches among gates operating at different rates. These issues collectively necessitate specialized operational expertise and controlled conditions, thus undermining the potential of molecular logic systems as deployable "smart" sensors.

5.3.3 Biocompatibility and the *in vivo* challenge. For biomedical applications, biocompatibility represents a significant challenge. Native nucleic acids are highly susceptible to rapid degradation by nucleases found in biological fluids, such as serum nucleases in blood.[270] Similarly, protein-based components are susceptible to proteolysis, which considerably diminishes their functional longevity *in vivo*. Furthermore, the introduction of exogenous molecular components can elicit immune responses, leading to inflammatory reactions and premature clearance from the body. Efficient intracellular delivery is yet another substantial barrier; achieving cell-specific targeting often requires encapsulation within delivery vehicles, such as lipid nanoparticles or viral vectors,[271,272] which can introduce additional complexities and potential toxicities. As a result, a system that demonstrates strong performance *in vitro* may fail *in vivo* unless purposefully engineered to function within the intricacies of a biological environment. Thus, prioritizing strategies to enhance biocompatibility and stability, such as the biochemical modification of nucleotides, should be a focal point for future research.

5.3.4 The performance chasm. Although academic reports frequently highlight successful logic operations, they often overlook critical performance shortcomings. For instance, molecular logic gates typically operate at slow speeds limited by diffusion kinetics,[273] making them inadequate for real-time diagnostics or monitoring applications. Signal outputs – often optical – tend to exhibit low intensity, high background noise, and significant attenuation when gates are cascaded, reducing reliability in practical settings. Moreover, a fluorescence change that is statistically significant in controlled experiments may be imperceptible to human observation or incompatible with low-cost sensors. Reproducibility across different synthesis batches remains another substantial, yet frequently unaddressed, challenge-hindering consistent large-scale implementation and validation.

The above challenges related to cost, operational complexity, biocompatibility, and performance collectively underscore a deeper issue: the "pragmatism gap" between theoretical demonstration and practical utility. Bridging this gap requires a shift in focus from molecular computation as an end in itself to molecular engineering as an application-driven discipline. The goal should not be to compete with silicon-based computing, but to exploit the unique capabilities of molecular systems such as their ability to sense and respond intelligently within biochemical environments. Future breakthroughs will likely arise from the design of simple, robust, and efficient logic-gated systems that outperform existing solutions in real-world scenarios. Achieving this will necessitate realigned research priorities, strategic funding, and a redefinition of success to emphasize applicability, scalability, and translational impact.

6 Conclusions

Molecular logic computing toolkits are advancing rapidly in the bioanalytical and biomedical research fields. These molecular logic operations can detect multiple input signals within complex environments by utilizing modular multi-signal integration, activatable locking key (OFF–ON) reconfigurable control and programmable control of multiple toolkit features. This permits effective analysis and integration of input signals, ultimately generating concise and clear output signals. This review focuses on summarizing the construction and functionality of smart molecular logic computing toolkits in nucleic acid-associated biosensing, highlighting significant advancements in analytical sensing strategies, functionalities and their applications.

Although molecular logic systems have advanced from basic Boolean gates to complex circuits that can process intricate biomarker profiles, their translation from proof-of-concept into practical applications remains limited by key interdisciplinary challenges. Herein, we delineate these major barriers and present a forward-looking perspective on potential strategies to address them.

6.1 Enhancing signal integrity and noise resilience in biological environments

A central challenge in deploying molecular logic systems under physiological conditions stems from the inherently stochastic and diffusion, limited nature of biochemical signaling. In complex cellular or tissue environments, molecular circuits are prone to signal attenuation, inter-pathway crosstalk, and kinetic delays, issues that become increasingly pronounced in multi-layered or cascaded network architectures. To mitigate these effects, next-generation systems should integrate AI-enhanced noise suppression strategies, such as recurrent neural networks for real-time signal denoising or convolutional models for deconvolving multiplexed outputs in spectrally overlapping assays. Further gains in reliability may be achieved by embedding kinetic proofreading mechanisms and non-equilibrium dynamic circuit designs, which can significantly reduce false-positive rates and improve operational specificity under low signal-to-noise conditions.

6.2 Scalability and interoperability in multi-layer circuit design

A major bottleneck in scaling molecular logic systems is the absence of a plug-and-play architectural framework, which hinders modular integration and seamless interoperability between components. Constraints such as limited fan-out and fan-in capacity in individual logic gates restrict the development of complex cascaded circuits, while the lack of standardized signal translators complicates communication between disparate sensing modules. To address these issues, the field should prioritize the establishment of modular bio-interfaces based on universal optical, electrochemical, or plasmonic reporting mechanisms. When combined with AI-driven circuit routing algorithms, such platforms can enable autonomous optimization of inter-gate connectivity and support dynamic reconfiguration—essential advances toward scalable, multiplexed diagnostic systems capable of decoding complex disease signatures.

6.3 Clinical translation through portable and autonomous platforms

A critical barrier to the clinical impact of molecular logic is its current reliance on benchtop instrumentation, which limits practical deployment. To overcome this, future efforts must focus on the convergence of hardware and software: integrating functional biomolecular circuits with wearable microsensors and miniaturized readers equipped with onboard AI for real-time, point-of-need decision-making. Such platforms will enable continuous, closed-loop monitoring of complex biomarkers. Beyond this, pioneering endogenous energy harvesting, from sources such as ATP, glucose, or other metabolites, will be transformative, paving the way for fully self-sustaining, implantable systems capable of intelligent and adaptive therapy. This represents the ultimate frontier in personalized medicine.

6.4 AI-guided design and context-aware logic

Biological environments present a formidable challenge for molecular circuits due to their inherent complexity and dynamic nature. Factors such as fluctuating pH, variable metabolite concentrations, enzymatic degradation, and off-target interactions create a noisy and unpredictable operational landscape. A central challenge in molecular computing lies in overcoming the static nature of pre-defined circuits to create systems that are truly adaptive to their complex biological environments. The integration of machine learning, particularly generative models and reinforcement learning, is key to achieving this breakthrough. It will enable the accurate prediction of nucleic acid behavior and circuit interactions, thereby engineering systems that dynamically interpret contextual cues. This advancement will unlock sophisticated capabilities, from tissue-specific activation and biomarker-weighted decision-making to closed-loop cellular control.

In summary, while molecular logic-based biosensing holds considerable promise, its practical deployment remains constrained by issues of robustness, scalability, and real-world integration. In the near term, progress will depend critically on integrating machine learning-assisted circuit design to improve dynamic response and system compatibility, alongside hybrid material platforms that enhance signal amplification and operational stability. Looking forward, molecular logic is poised to transition from a laboratory tool to an integral part of intelligent point-of-care diagnostics and closed-loop therapeutic systems. The field is moving toward embedded bioanalytical devices capable of detecting complex biomarker panels directly from clinical samples with high specificity. Advances in AI-guided design and modular sensor integration are catalyzing the development of context-aware molecular systems that will ultimately enable autonomous diagnostics and personalized medicine. Near-term efforts will likely focus

on hybrid bio–electronic interfaces that combine molecular recognition with electronic readout and AI-enhanced data processing. In the longer term, the convergence of synthetic biology, functional nanomaterials, and machine learning could give rise to autonomous molecular processors capable of real-time health monitoring, adaptive drug delivery, and early disease diagnosis. Through sustained innovation in molecular design, signal processing, and system integration, molecular logic is positioned to become a cornerstone of next-generation precision medicine.

Author contributions

Y. Hu: investigation, methodology, data curation, formal analysis, writing – original draft. J. Zhang: conceptualization, methodology, resources, formal analysis, visualization, supervision, funding acquisition, writing – original draft. K. Shen: software, investigation, visualization. W. Shen: supervision, methodology, validation, visualization. H. K. Lee: resources, supervision, writing – review & editing. S. Tang: project administration, resources, supervision, writing – review & editing.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Acknowledgements

The authors are grateful for financial support from the National Natural Science Foundation of China (Grant No. 22204064, 22276080, 22574067 and W2431017), the Natural Science Foundation of Jiangsu Province, China (Grant No. BK20220645) and Key Research and Development Program of Zhenjiang, China (Grant No. SH2023103).

Notes and references

1 J. Son, J. Jeon, K. Cho and S. Kim, Stateful logic operation of gated silicon diodes for in-memory computing, *Adv. Electron. Mater.*, 2024, **10**, 2300815.
2 M. Gonzalez-Zalba, S. De Franceschi, E. Charbon, T. Meunier, M. Vinet and A. Dzurak, Scaling silicon-based quantum computing using CMOS technology, *Nat. Electron.*, 2021, **4**, 872–884.
3 T. He, H. Ma, Z. Wang, Q. Li, S. Liu, S. Duan, T. Xu, J. Wang, H. Wu and F. Zhong, On-chip optoelectronic logic gates operating in the telecom band, *Nat. Photonics*, 2024, **18**, 60–67.
4 A. P. De Silva and S. Uchiyama, Molecular logic and computing, *Nat. Nanotechnol.*, 2007, **2**, 399–410.
5 G. E. Moore, Cramming more components onto integrated circuits, reprinted from electronics, *IEEE J. Solid State Circ.*, 2006, **11**, 33–35.
6 S. E. Thompson and S. Parthasarathy, Moore's law: the future of Si microelectronics, *Mater. Today*, 2006, **9**, 20–25.
7 E. U. Akkaya, E. Katz and U. Pischel, Molecular logic: from single logic gates to sophisticated logic circuits, from fundamental science to practical applications, *ChemPhysChem*, 2017, **18**, 1665–1666.
8 C. Kieffer, A. J. Genot, Y. Rondelez and G. Gines, Molecular computation for molecular classification, *Adv. Biol.*, 2023, **7**, 2200203.
9 S. Erbas-Cakmak, S. Kolemen, A. C. Sedgwick, T. Gunnlaugsson, T. D. James, J. Yoon and E. U. Akkaya, Molecular logic gates: the past, present and future, *Chem. Soc. Rev.*, 2018, **47**, 2228–2248.
10 K. He, Y. Li, B. Xiang, P. Zhao, Y. Hu, Y. Huang, W. Li, Z. Nie and S. Yao, A universal platform for building molecular logic circuits based on a reconfigurable three-dimensional DNA nanostructure, *Chem. Sci.*, 2015, **6**, 3556–3564.
11 P. A. De Silva, N. H. Gunaratne and C. P. McCoy, A molecular photoionic AND gate based on fluorescent signalling, *Nature*, 1993, **364**, 42–44.
12 D. Bose, G. A. Kaur, S. Balayan, S. Chatterjee and A. Tiwari, The logic devices for biomolecular computing: Progress, strategies, and future directions, *Nano Today*, 2024, **57**, 102320.
13 K. Wang, S. Liu, S. Zhou, A. Qileng, D. Wang, Y. Liu, C. Chen, C. Lei and Z. Nie, Ligand-responsive artificial protein-protein communication for field-deployable cell-free biosensing, *Angew. Chem., Int. Ed.*, 2025, **137**, e202416671.
14 T. Jiang, Y. Teng, C. Li, Q. Gan, J. Zhang, Y. Zou, B. K. Desai and Y. Yan, Establishing tunable genetic logic gates with versatile dynamic performance by varying regulatory parameters, *ACS Synth. Biol.*, 2023, **12**, 3730–3742.
15 J. Bonnet, P. Yin, M. E. Ortiz, P. Subsoontorn and D. Endy, Amplifying genetic logic gates, *Science*, 2013, **340**, 599–603.
16 G. G. Dias and F. T. Souto, Architecture of molecular logic gates: from design to application as optical detection devices, *Organics*, 2024, **5**, 114–162.
17 Y. Benenson, Biomolecular computing systems: principles, progress and potential, *Nat. Rev. Genet.*, 2012, **13**, 455–468.
18 Y. Yang, J. Xu, Y. Sun, L. Mo, B. Liu, X. Pan, Z. Liu and W. Tan, Aptamer-based logic computing reaction on living cells to enable non-antibody immune checkpoint blockade therapy, *J. Am. Chem. Soc.*, 2021, **143**, 8391–8401.
19 H. M. Junaid, M. T. Waseem, Z. A. Khan, F. Munir, S. Sohail, U. Farooq and S. A. Shahzad, Fluorenone-based fluorescent and colorimetric sensors for selective detection of I^- ions: applications in hela cell imaging and logic gate, *ACS Omega*, 2022, **7**, 9730–9742.
20 D. C. Magri, Logical sensing with fluorescent molecular logic gates based on photoinduced electron transfer, *Coord. Chem. Rev.*, 2021, **426**, 213598.

21 S. Stangherlin, N. Lui, J. H. Lee and J. Liu, Aptamer-based biosensors: from SELEX to biomedical diagnostics, *TrAC Trends Anal. Chem.*, 2025, **191**, 118349.
22 C. Willmott and J. Bryant, Genomics is here: what can we do with it, and what ethical issues has it brought along for the ride?, *New Bioeth.*, 2023, **29**, 1–9.
23 P. Amaral, S. Carbonell-Sala, F. M. De La Vega, T. Faial, A. Frankish, T. Gingeras, R. Guigo, J. L. Harrow, A. G. Hatzigeorgiou and R. Johnson, The status of the human gene catalogue, *Nature*, 2023, **622**, 41–47.
24 P. Pokhrel, C. Hu and H. Mao, Detecting the coronavirus (COVID-19), *ACS Sens.*, 2020, **5**, 2283–2296.
25 Y. Zhu, M. Zhang, Z. Jie and S. Tao, Nucleic acid testing of SARS-CoV-2: A review of current methods, challenges, and prospects, *Front. Microbiol.*, 2022, **13**, 1074289.
26 Y. Li, J. Zhang, J. Chen, F. Zhu, Z. Liu, P. Bao, W. Shen and S. Tang, Detection of SARS-CoV-2 based on artificial intelligence-assisted smartphone: A review, *Chin. Chem. Lett.*, 2024, **35**, 109220.
27 A. Shibata, S. L. Higashi and M. Ikeda, Nucleic acid-based fluorescent sensor systems: A review, *Polym. J.*, 2022, **54**, 751–766.
28 L.-Z. Kong, S.-M. Kim, C. Wang, S. Y. Lee, S.-C. Oh, S. Lee, S. Jo and T.-D. Kim, Understanding nucleic acid sensing and its therapeutic applications, *Exp. Mol. Med.*, 2023, **55**, 2320–2331.
29 Y.-L. Ying, Z.-L. Hu, S. Zhang, Y. Qing, A. Fragasso, G. Maglia, A. Meller, H. Bayley, C. Dekker and Y.-T. Long, Nanopore-based technologies beyond DNA sequencing, *Nat. Nanotechnol.*, 2022, **17**, 1136–1146.
30 C. Cao, D.-F. Liao, J. Yu, H. Tian and Y.-T. Long, Construction of an aerolysin nanopore in a lipid bilayer for single-oligonucleotide analysis, *Nat. Protoc.*, 2017, **12**, 1901–1911.
31 Z. Ma, J. Xu, W. Hou, Z. Lei, T. Li, W. Shen, H. Yu, C. Liu, J. Zhang and S. Tang, Detection of single nucleotide polymorphisms of circulating tumor DNA by strand displacement amplification coupled with liquid chromatography, *Anal. Chem.*, 2024, **96**, 5195–5204.
32 M. Song, J. Zhang, K. Shen, Y. Hu, W. Shen, S. Tang and H. K. Lee, Application of smart-responsive hydrogels in nucleic acid and nucleic acid-based target sensing: A review, *Biosens. Bioelectron.*, 2024, 116803.
33 Y. Zhao, X. Li, Y. Zhou, X. Tian, Y. Miao, J. Wang, L. Huang and F. Meng, Advancements in DNA computing: exploring DNA logic systems and their biomedical applications, *J. Mater. Chem. B*, 2024, **12**, 10134–10148.
34 F. Yin, F. Wang, C. Fan, X. Zuo and Q. Li, Biosensors based on DNA logic gates, *View*, 2021, **2**, 20200038.
35 L. Liu, P. Liu, L. Ga and J. Ai, Advances in applications of molecular logic gates, *ACS Omega*, 2021, **6**, 30189–30204.
36 D. Fan, J. Wang, E. Wang and S. Dong, Propelling DNA computing with materials' power: Recent advancements in innovative DNA logic computing systems and smart bio-applications, *Adv. Sci.*, 2020, **7**, 2001766.
37 L. Zhang, H. Yang, Y. Yan, H. Zhao, D. Han and X. Su, A multi-input molecular classifier based on digital DNA strand displacement for disease diagnostics, *Adv. Mater.*, 2025, **37**, 2413198.
38 D. Kong, S. Zhang, X. Ma, Y. Yang, C. Dai, L. Geng, Y. Liu and D. Wei, DNA logical computing on a transistor for cancer molecular diagnosis, *Angew. Chem., Int. Ed.*, 2024, **63**, e202407039.
39 L. Qian and E. Winfree, Scaling up digital circuit computation with DNA strand displacement cascades, *Science*, 2011, **332**, 1196–1201.
40 X. Liu, Z. Chen, K. Wan, Y. Luo, J. Yang, L. Li, K. Tao, X. Xiao and M. Zhang, Highly reusable enzyme-driven DNA logic circuits, *ACS Nano*, 2025, **19**, 9906–9914.
41 A. Armstrong and M. Isalan, Engineering bacterial theranostics: from logic gates to *in vivo* applications, *Front. Bioeng. Biotechnol.*, 2024, **12**, 1437301.
42 A. S. Khalil and J. J. Collins, Synthetic biology: applications come of age, *Nat. Rev. Genet.*, 2010, **11**, 367–379.
43 P. Zhang, D. Gao, K. An, Q. Shen, C. Wang, Y. Zhang, X. Pan, X. Chen, Y. Lyv, C. Cui, T. Liang, X. Duan, J. Liu, T. Yang, X. Hu, J.-J. Zhu, F. Xu and W. Tan, A programmable polymer library that enables the construction of stimuli-responsive nanocarriers containing logic gates, *Nat. Chem.*, 2020, **12**, 381–390.
44 R. Fu, J. Hou, Z. Wang and Y. Xianyu, DNA molecular computation using the CRISPR-mediated reaction and surface growth of gold nanoparticles, *ACS Nano*, 2024, **18**, 14754–14763.
45 D. Wang, S. Li, Z. Zhao, X. Zhang and W. Tan, Engineering a second-order DNA logic-gated nanorobot to sense and release on live cell membranes for multiplexed diagnosis and synergistic therapy, *Angew. Chem., Int. Ed.*, 2021, **60**, 15816–15820.
46 R. Tang, Y.-H. Fu, B. Gong, Y.-Y. Fan, H.-H. Wang, Y. Huang, Z. Nie and P. Wei, A chimeric conjugate of antibody and programmable DNA nanoassembly smartly activates T cells for precise cancer cell targeting, *Angew. Chem., Int. Ed.*, 2022, **61**, e202205902.
47 Q. Yang, Z.-L. Song, W. Xin, X. Lu, G.-C. Fan and X. Luo, Self-delivered boolean logic DNA nanoassembly for precision activation of cGAS-STING pathway and cancer-selective cytotoxicity, *CCS Chem.*, 2025, DOI: **10.31635/ccschem.025.202505810**.
48 G. Seelig, D. Soloveichik, D. Y. Zhang and E. Winfree, Enzyme-free nucleic acid logic circuits, *Science*, 2006, **314**, 1585–1588.
49 X. Xiong, M. Xiao, W. Lai, L. Li, C. Fan and H. Pei, Optochemical control of DNA-switching circuits for logic and probabilistic computation, *Angew. Chem., Int. Ed.*, 2021, **60**, 3397–3401.
50 S. Wang, Z. Zhang, R. Tang, F. He, Y. Huang, Z. Nie and C. Lei, Responsive MXene nanovehicles deliver CRISPR/Cas12a for boolean logic-controlled gene editing, *Sci. China:Chem.*, 2022, **65**, 2318–2326.
51 M. Hu, T. Xie, Y. Hu, L. Li, T. Wang and T. Wu, Allosteric DNAzyme-based encoder for molecular information transfer, *Chin. Chem. Lett.*, 2024, **35**, 109232.

52 C. Huang, J. Shao, B. Peng, Q. Guo, P. Li, J. Sun and Y. Wang, Design of a universal decoder model based on DNA winner-takes-all neural networks, *IEEE Trans. Comput.*, 2025, **74**, 1267–1277.
53 T. Xie, Y. Deng, J. Zhang, Z. Zhang, Z. Hu and T. Wu, DNA circuits compatible encoder and demultiplexer based on a single biomolecular platform with DNA strands as outputs, *Nucleic Acids Res.*, 2022, **50**, 8431–8440.
54 M. Hu, X. Li, J.-n. Wu, M. Yang and T. Wu, DNAzyme-based dissipative DNA strand displacement for constructing temporal logic gates, *ACS Nano*, 2024, **18**, 2184–2194.
55 T. Xie, C. Li, M. Hu, X. Zhong, J. Xiao, Z. Zhang, Z. Wang and T. Wu, DNA sequential logic circuits for reversible counters and dynamic biomolecular sensing, *Adv. Sci.*, 2025, e05793.
56 A. P. Lapteva, N. Sarraf and L. Qian, DNA strand-displacement temporal logic circuits, *J. Am. Chem. Soc.*, 2022, **144**, 12443–12449.
57 K. Shi, S. Xie, R. Tian, S. Wang, Q. Lu, D. Gao, C. Lei, H. Zhu and Z. Nie, A CRISPR-Cas autocatalysis-driven feedback amplification network for supersensitive DNA diagnostics, *Sci. Adv.*, 2021, **7**, eabc7802.
58 J. Kim and E. Winfree, Synthetic *in vitro* transcriptional oscillators, *Mol. Syst. Biol.*, 2011, **7**, 465.
59 Z. Zhou, N. Lin, Y. Ouyang, S. Liu, Y. Zhang and I. Willner, Cascaded, feedback-driven, and spatially localized emergence of constitutional dynamic networks driven by enzyme-free catalytic DNA circuits, *J. Am. Chem. Soc.*, 2023, **145**, 12617–12629.
60 J. Y. Lu, Q. Jiang, J. J. Lei, Y. X. He and W. T. Huang, Molecular 'email': electrochemical aptasensing of fish pathogens, molecular information encoding, encryption and hiding applications, *Anal. Chim. Acta*, 2022, **1232**, 340483.
61 J. Y. Lu, Z. X. Xie, J. Zhou, M. Y. Wu, Y. Q. Tian, T. T. Fu, D. H. Wang, B. S. He and W. T. Huang, Multifunctional antimonene-gold nanocomposites for fluorescence sensing of exosomes and metal ions, molecular information encoding and protection, *Adv. Compos. Hybrid Mater.*, 2025, **8**, 329.
62 W. T. Huang, J. R. Zhang, W. Y. Xie, Y. Shi, H. Q. Luo and N. B. Li, Fuzzy logic sensing of G-quadruplex DNA and its cleavage reagents based on reduced graphene oxide, *Biosens. Bioelectron.*, 2014, **57**, 117–124.
63 W. T. Huang, H. Q. Luo and N. B. Li, Boolean logic tree of graphene-based chemical system for molecular computation and intelligent molecular search query, *Anal. Chem.*, 2014, **86**, 4494–4500.
64 Q. Y. Zhu, F. R. Zhang, Y. Du, X. X. Zhang, J. Y. Lu, Q. F. Yao, W. T. Huang, X. Z. Ding and L. Q. Xia, Graphene-based steganographically aptasensing system for information computing, encryption and hiding, fluorescence sensing and *in vivo* imaging of fish pathogens, *ACS Appl. Mater. Interfaces*, 2019, **11**, 8904–8914.
65 J. Zhou, Y. Wu, Z. X. Xie, J. Y. Lu and W. T. Huang, Sequential-dependent synthesis of gold-chromium nanocomposites for multimode colorimetric sensing, advanced logic computing, and tri-layer information protection, *Chem. Eng. J.*, 2024, **497**, 154725.
66 A. Bérut, A. Arakelyan, A. Petrosyan, S. Ciliberto, R. Dillenschneider and E. Lutz, Experimental verification of Landauer's principle linking information and thermodynamics, *Nature*, 2012, **483**, 187–189.
67 T. Li, F. Lohmann and M. Famulok, Interlocked DNA nanostructures controlled by a reversible logic circuit, *Nat. Commun.*, 2014, **5**, 4940.
68 X. Song and J. Reif, Nucleic acid databases and molecular-scale computing, *ACS Nano*, 2019, **13**, 6256–6268.
69 Y. Zhang, N. Hu, J. Xu and Z. Wang, DNA logic programming: from concept to construction, *View*, 2024, **5**, 20230062.
70 Y. Yin, W. Xie, M. Xiong, Y. Gao, Q. Liu, D. Han, G. Ke and X. B. Zhang, Finder: A fluidly confined CRISPR-based DNA reporter on living cell membranes for rapid and sensitive cancer cell identification, *Angew. Chem., Int. Ed.*, 2023, **62**, e202309837.
71 A. Padirac, T. Fujii and Y. Rondelez, Bottom-up construction of *in vitro* switchable memories, *Proc. Natl. Acad. Sci. U. S. A.*, 2012, **109**, E3212–E3220.
72 L. M. Adleman, Molecular computation of solutions to combinatorial problems, *Science*, 1994, **266**, 1021–1024.
73 M. Zhang and D. Han, Concept, development and applications of DNA computation, *Fundam. Res.*, 2023, DOI: **10.1016/j.fmre.2023.06.015**.
74 R. J. Lipton, DNA solution of hard computational problems, *Science*, 1995, **268**, 542–545.
75 S. Jia, H. Lv, Q. Li, C. Fan and F. Wang, DNA-based biocomputing circuits and their biomedical applications, *Nat. Rev. Bioeng.*, 2025, **3**, 535–548.
76 T. Song, A. Eshra, S. Shah, H. Bui, D. Fu, M. Yang, R. Mokhtar and J. Reif, Fast and compact DNA logic circuits based on single-stranded gates using strand-displacing polymerase, *Nat. Nanotechnol.*, 2019, **14**, 1075–1081.
77 A. Bertucci, A. Porchetta, E. Del Grosso, T. Patiño, A. Idili and F. Ricci, Protein-controlled actuation of dynamic nucleic acid networks by using synthetic DNA translators, *Angew. Chem., Int. Ed.*, 2020, **59**, 20577–20581.
78 M. R. Dunn, R. M. Jimenez and J. C. Chaput, Analysis of aptamer discovery and technology, *Nat. Rev. Chem.*, 2017, **1**, 0076.
79 S. Liu, X. Li, H. Gao, J. Chen and H. Jiang, Progress in aptamer research and future applications, *ChemistryOpen*, 2025, e202400463.
80 K. Sefah, D. Shangguan, X. Xiong, M. B. O'donoghue and W. Tan, Development of DNA aptamers using Cell-SELEX, *Nat. Protoc.*, 2010, **5**, 1169–1185.
81 L. Li, X. Chen, C. Cui, X. Pan, X. Li, H. S. Yazd, Q. Wu, L. Qiu, J. Li and W. Tan, Aptamer displacement reaction from live-cell surfaces and its applications, *J. Am. Chem. Soc.*, 2019, **141**, 17174–17179.
82 Q.-L. Zhang, L.-L. Wang, Y. Liu, J. Lin and L. Xu, A kinetically controlled platform for ligand-oligonucleotide transduction, *Nat. Commun.*, 2021, **12**, 4654.

83 Q. L. Zhang, Y. Wang, L. L. Wang, F. Xie, R. Y. Wu, X. Y. Ma, H. Li, Y. Liu, S. Yao and L. Xu, Programming non-nucleic acid molecules into computational nucleic acid systems, *Angew. Chem., Int. Ed.*, 2023, **135**, e202214698.
84 X. Chang, C. Zhang, C. Lv, Y. Sun, M. Zhang, Y. Zhao, L. Yang, D. Han and W. Tan, Construction of a multiple-aptamer-based DNA logic device on live cell membranes *via* associative toehold activation for accurate cancer cell identification, *J. Am. Chem. Soc.*, 2019, **141**, 12738–12743.
85 D. Wang, S. Li, Z. Zhao, X. Zhang and W. Tan, Engineering a second-order DNA logic-gated nanorobot to sense and release on live cell membranes for multiplexed diagnosis and synergistic therapy, *Angew. Chem., Int. Ed.*, 2021, **60**, 15816–15820.
86 S. Liu, J. Ding and W. Qin, Dual-analyte chronopotentiometric aptasensing platform based on a G-quadruplex/hemin DNAzyme and logic gate operations, *Anal. Chem.*, 2019, **91**, 3170–3176.
87 D. Morrison, M. Rothenbroker and Y. Li, DNAzymes: selected for applications, *Small Methods*, 2018, **2**, 1700319.
88 Y. Zhou and C. Zhou, Designing *in vivo* active DNAzymes, *Nat. Chem.*, 2021, **13**, 299–301.
89 P. J. J. Huang, D. de Rochambeau, H. F. Sleiman and J. Liu, Target self-enhanced selectivity in metal-specific DNAzymes, *Angew. Chem., Int. Ed.*, 2020, **132**, 3601–3605.
90 M. N. Stojanovic, T. E. Mitchell and D. Stefanovic, Deoxyribozyme-based logic gates, *J. Am. Chem. Soc.*, 2002, **124**, 3555–3561.
91 M. N. Stojanovic and D. Stefanovic, A deoxyribozyme-based molecular automaton, *Nat. Biotechnol.*, 2003, **21**, 1069–1074.
92 D. M. Kolpashchikov and M. N. Stojanovic, Boolean control of aptamer binding states, *J. Am. Chem. Soc.*, 2005, **127**, 11348–11351.
93 R. Pei, E. Matamoros, M. Liu, D. Stefanovic and M. N. Stojanovic, Training a molecular automaton to play a game, *Nat. Nanotechnol.*, 2010, **5**, 773–777.
94 B. Wang, M. Wang, F. Peng, X. Fu, M. Wen, Y. Shi, M. Chen, G. Ke and X.-B. Zhang, Construction and application of DNAzyme-based nanodevices, *Chem. Res. Chin. Univ.*, 2023, **39**, 42–60.
95 R. Liu, D. Jiang, Y. Yun, Z. Feng, F. Zheng, Y. Xiang, H. Fan and J. Zhang, Photoactivatable engineering of CRISPR/Cas9-Inducible DNAzyme probe for *In situ* imaging of nuclear zinc ions, *Angew. Chem., Int. Ed.*, 2024, **136**, e202315536.
96 T. Xu, F. Li, Y. Jin, F. Jia, Y. Wang, T. Lv, Y. Zhang, M. Li, C. Fan and M. Li, Framework nucleic acid-mediated DNAzyme chaperoning for sensitive trace metal ion mapping on live neuronal cell membranes, *Angew. Chem., Int. Ed.*, 2025, **64**, e202506640.
97 Z. Wang, J. Yang, G. Qin, C. Zhao, J. Ren and X. Qu, An intelligent nanomachine guided by DNAzyme logic system for precise chemodynamic therapy, *Angew. Chem., Int. Ed.*, 2022, **61**, e202204291.
98 N. Srinivas, J. Parkin, G. Seelig, E. Winfree and D. Soloveichik, Enzyme-free nucleic acid dynamical systems, *Science*, 2017, **358**, eaal2052.
99 F. Wang, H. Lv, Q. Li, J. Li, X. Zhang, J. Shi, L. Wang and C. Fan, Implementing digital computing with DNA-based switching circuits, *Nat. Commun.*, 2020, **11**, 121.
100 T. Mayer, L. Oesinghaus and F. C. Simmel, Toehold-mediated strand displacement in random sequence pools, *J. Am. Chem. Soc.*, 2022, **145**, 634–644.
101 L. Tang, T. Luo, S. Fan, Y. Liu and J. Song, Principles of nucleic acid toehold mediated strand displacement (TMSD) reaction model and its applications in cell environment, *Biomater. Sci.*, 2023, **11**, 5060–5077.
102 J. K. Jung, C. M. Archuleta, K. K. Alam and J. B. Lucks, Programming cell-free biosensors with DNA strand displacement circuits, *Nat. Chem. Biol.*, 2022, **18**, 385–393.
103 W. Y. Lv, L. L. Li, C. Y. Guan, C. M. Li, C. Z. Huang and S. J. Zhen, Rational design of cascade DNA system for signal amplification, *Anal. Chem.*, 2023, **95**, 7603–7610.
104 P. Miao and Y. Tang, Cascade strand displacement and bipedal walking based DNA logic system for miRNA diagnostics, *ACS Cent. Sci.*, 2021, **7**, 1036–1044.
105 N. V. Dokholyan, Nanoscale programming of cellular and physiological phenotypes: inorganic meets organic programming, *npj Syst. Biol. Appl.*, 2021, **7**, 15.
106 A. A. Green, J. Kim, D. Ma, P. A. Silver, J. J. Collins and P. Yin, Complex cellular logic computation using ribocomputing devices, *Nature*, 2017, **548**, 117–121.
107 A. A. Nielsen, B. S. Der, J. Shin, P. Vaidyanathan, V. Paralanov, E. A. Strychalski, D. Ross, D. Densmore and C. A. Voigt, Genetic circuit design automation, *Science*, 2016, **352**, aac7341.
108 O. Dagliyan, M. Tarnawski, P.-H. Chu, D. Shirvanyants, I. Schlichting, N. V. Dokholyan and K. M. Hahn, Engineering extrinsic disorder to control protein activity in living cells, *Science*, 2016, **354**, 1441–1444.
109 Y. Gao, R. Mardian, J. Ma, Y. Li, C. E. French and B. Wang, Programmable trans-splicing riboregulators for complex cellular logic computation, *Nat. Chem. Biol.*, 2025, **21**, 758–766.
110 A. P. Teixeira and M. Fussenegger, Synthetic macromolecular switches for precision control of therapeutic cell functions, *Nat. Rev. Bioeng.*, 2024, **2**, 1005–1022.
111 A. Didovyk and L. S. Tsimring, Synthetic gene circuits learn to classify, *Cell Syst.*, 2017, **4**, 151–153.
112 P. Mohammadi, N. Beerenwinkel and Y. Benenson, Automated design of synthetic cell classifier circuits using a two-step optimization strategy, *Cell Syst.*, 2017, **4**, 207–218.
113 J. Stricker, S. Cookson, M. R. Bennett, W. H. Mather, L. S. Tsimring and J. Hasty, A fast, robust and tunable synthetic gene oscillator, *Nature*, 2008, **456**, 516–519.
114 R.-Y. Wu, C.-Q. Wu, F. Xie, X. Xing and L. Xu, Building RNA-mediated artificial signaling pathways between endogenous genes, *Acc. Chem. Res.*, 2024, **57**, 1777–1789.

115 V. K. Mutalik, L. Qi, J. C. Guimaraes, J. B. Lucks and A. P. Arkin, Rationally designed families of orthogonal RNA regulators of translation, *Nat. Chem. Biol.*, 2012, **8**, 447–454.

116 R. A. Wesselhoeft, P. S. Kowalski and D. G. Anderson, Engineering circular RNA for potent and stable translation in eukaryotic cells, *Nat. Commun.*, 2018, **9**, 2629.

117 A. A. Green, P. A. Silver, J. J. Collins and P. Yin, Toehold switches: De-novo-designed regulators of gene expression, *Cell*, 2014, **159**, 925–939.

118 J. Kim, Y. Zhou, P. D. Carlson, M. Teichmann, S. Chaudhary, F. C. Simmel, P. A. Silver, J. J. Collins, J. B. Lucks and P. Yin, De novo-designed translation-repressing riboregulators for multi-input cellular logic, *Nat. Chem. Biol.*, 2019, **15**, 1173–1182.

119 K.-H. Siu and W. Chen, Riboregulated toehold-gated gRNA for programmable CRISPR-Cas9 function, *Nat. Chem. Biol.*, 2019, **15**, 217–220.

120 E. M. Zhao, A. S. Mao, H. de Puig, K. Zhang, N. D. Tippens, X. Tan, F. A. Ran, I. Han, P. Q. Nguyen, E. J. Chory, T. Y. Hua, P. Ramesh, D. B. Thompson, C. Y. Oh, E. S. Zigon, M. A. English and J. J. Collins, RNA-responsive elements for eukaryotic translational control, *Nat. Biotechnol.*, 2022, **40**, 539–545.

121 S. Matsuura, H. Ono, S. Kawasaki, Y. Kuang, Y. Fujita and H. Saito, Synthetic RNA-based logic computation in mammalian cells, *Nat. Commun.*, 2018, **9**, 4847.

122 Z. He, C. Liu, Z. Li, Z. Chu, X. Chen, X. Chen and Y. Guo, Advances in the use of nanomaterials for nucleic acid detection in point-of-care testing devices: A review, *Front. Bioeng. Biotechnol.*, 2022, **10**, 1020444.

123 X. Wang, F. Li and Y. Guo, Recent trends in nanomaterial-based biosensors for point-of-care testing, *Front. Chem.*, 2020, **8**, 586702.

124 B. Yan, Multiple luminescence responsive chemical sensing of lanthanide functionalized metal-organic frameworks hybrids for logic gate operation application to construct intelligent detecting platform, *TrAC Trends Anal. Chem.*, 2024, **170**, 117430.

125 Z. Liu, Q. Gao, W. Shen, M. Xu, Y. Li, W. Hou, H.-W. Shi, Y. Yuan, E. Adams and H. K. Lee, Removal and fluorescence detection of antibiotics from wastewater by layered double oxides/metal-organic frameworks with different topological configurations, *Chin. Chem. Lett.*, 2024, **35**, 109338.

126 M. Zandieh, J. H. Lee and J. Liu, DNA attachment to polymeric, soft and quantum materials: mechanisms and applications, *Chem. Sci.*, 2025, **16**, 14865–14883.

127 L. Pang, X. Tang, L. Yao, L. Zhou, S. Hu, S. Zhao and L. Zhang, Smart down/upconversion nanomachines integrated with "AND" logic computation and enzyme-free amplification for NIR-II fluorescence-assisted precise and enhanced photodynamic therapy, *Chem. Sci.*, 2023, **14**, 3070–3075.

128 C. Zhang, M. Wu, S. Hu, S. Shi, Y. Duan, W. Hu and Y. Li, Label-free, high-throughput, sensitive, and logical analysis using biomimetic array based on stable luminescent copper nanoclusters and entropy-driven nanomachine, *Anal. Chem.*, 2023, **95**, 11978–11987.

129 M. P. Nikitin, V. O. Shipunova, S. M. Deyev and P. I. Nikitin, Biocomputing based on particle disassembly, *Nat. Nanotechnol.*, 2014, **9**, 716–722.

130 Y. Guo, J. Ren and E. Wang, Implementation of logic operations and bioanalysis based on DNA allostery-regulated nanometallic catalysis, *Nano Today*, 2022, **44**, 101476.

131 Z. Xie, L. Wroblewska, L. Prochazka, R. Weiss and Y. Benenson, Multi-input RNAi-based logic circuit for identification of specific cancer cells, *Science*, 2011, **333**, 1307–1311.

132 M. J. Lajoie, S. E. Boyken, A. I. Salter, J. Bruffey, A. Rajan, R. A. Langan, A. Olshefsky, V. Muhunthan, M. J. Bick and M. Gewe, Designed protein logic to target cells with precise combinations of surface antigens, *Science*, 2020, **369**, 1637–1643.

133 G. Chatterjee, N. Dalchau, R. A. Muscat, A. Phillips and G. Seelig, A spatially localized architecture for fast and modular DNA computing, *Nat. Nanotechnol.*, 2017, **12**, 920–927.

134 H. Kang, D. Park and J. Kim, Logical regulation of endogenous gene expression using programmable, multi-input processing CRISPR guide RNAs, *Nucleic Acids Res.*, 2024, **52**, 8595–8608.

135 Y. Li, P. Zhou, Z. Wang, Y. Ren, X. Zhu, J. Wang, H. Yan, L. Hua and F. Gao, Sea anemone-like nanomachine based on DNA strand displacement composed of three Boolean logic gates: Diversified input for intracellular multitarget detection, *Anal. Chem.*, 2024, **96**, 4120–4128.

136 J. H. Cho, J. J. Collins and W. W. Wong, Universal chimeric antigen receptors for multiplexed and logical control of T cell responses, *Cell*, 2018, **173**, 1426–1438.

137 H. R. Kempton, L. E. Goudy, K. S. Love and L. S. Qi, Multiple input sensing and signal integration using a split Cas12a system, *Mol. Cell*, 2020, **78**, 184–191.

138 S. M. Douglas, I. Bachelet and G. M. Church, A logic-gated nanorobot for targeted transport of molecular payloads, *Science*, 2012, **335**, 831–834.

139 M. Chen, C. Wang, Z. Ding, H. Wang, Y. Wang and Z. Liu, A molecular logic gate for developing "AND" logic probes and the application in hepatopathy differentiation, *ACS Cent. Sci.*, 2022, **8**, 837–844.

140 J. Wang, X. Han, H. Yu and G. Xie, AND logic-gate-based dual-locking probe system for the sensitive detection of microRNA and APE1, *Anal. Chem.*, 2024, **96**, 9570–9575.

141 K. Ren, Y. Liu, J. Wu, Y. Zhang, J. Zhu, M. Yang and H. Ju, A DNA dual lock-and-key strategy for cell-subtype-specific siRNA delivery, *Nat. Commun.*, 2016, **7**, 13580.

142 A. Fernandez, E. J. Thompson, J. W. Pollard, T. Kitamura and M. Vendrell, A fluorescent activatable AND-gate chemokine CCL2 enables *in vivo* detection of metastasis-associated macrophages, *Angew. Chem., Int. Ed.*, 2019, **58**, 16894–16898.

143 J. Zhang, Z. Qiu, J. Fan, F. He, W. Kang, S. Yang, H. H. Wang, J. Huang and Z. Nie, Scan and unlock:

a programmable DNA molecular automaton for cell-selective activation of ligand-based signaling, *Angew. Chem., Int. Ed.*, 2021, **133**, 6807–6817.

144 T. Song, S. Shah, H. Bui, S. Garg, A. Eshra, D. Fu, M. Yang, R. Mokhtar and J. Reif, Programming DNA-based biomolecular reaction networks on cancer cell membranes, *J. Am. Chem. Soc.*, 2019, **141**, 16539–16543.

145 X. Gong, J. Wei, J. Liu, R. Li, X. Liu and F. Wang, Programmable intracellular DNA biocomputing circuits for reliable cell recognitions, *Chem. Sci.*, 2019, **10**, 2989–2997.

146 Y. Li, S. Sun, L. Fan, S. Hu, Y. Huang, K. Zhang, Z. Nie and S. Yao, Peptide logic circuits based on chemoenzymatic ligation for programmable cell apoptosis, *Angew. Chem., Int. Ed.*, 2017, **56**, 14888–14892.

147 S. Chen, Z. Xu, W. Yang, X. Lin, J. Li, J. Li and H. Yang, Logic-gate-actuated DNA-controlled receptor assembly for the programmable modulation of cellular signal transduction, *Angew. Chem., Int. Ed.*, 2019, **131**, 18354–18358.

148 Z. Tian, D. Shao, L. Tang, Z. Li, Q. Chen, Y. Song, T. Li, F. C. Simmel and J. Song, Circular single-stranded DNA as a programmable vector for gene regulation in cell-free protein expression systems, *Nat. Commun.*, 2024, **15**, 4635.

149 X. Qu, S. Wang, Z. Ge, J. Wang, G. Yao, J. Li, X. Zuo, J. Shi, S. Song and L. Wang, Programming cell adhesion for on-chip sequential boolean logic functions, *J. Am. Chem. Soc.*, 2017, **139**, 10176–10179.

150 J. Tang, C. Ji, X. Lu, H. Cao, Y. Ling, Y. Wu, L. Qian, Y. He, B. Song and H. Wang, DNA origami plasmonic nanoantenna for programmable biosensing of multiple cytokines in cancer immunotherapy, *Anal. Chem.*, 2024, **96**, 9684–9692.

151 X.-Q. Li, Y.-L. Jia, Y.-W. Zhang, H.-Y. Chen and J.-J. Xu, Intracellular activated logic nanomachines based on framework nucleic acids for low background detection of microRNAs in living cells, *Chem. Sci.*, 2023, **14**, 7699–7708.

152 Q. Wang, R. Chang, X. Li, Y. Zhang, X. Fan, L. Shi and T. Li, Logic-gated DNA intelligent nanorobots for cellular lysosome interference and enhanced therapeutics, *Angew. Chem., Int. Ed.*, 2025, **64**, e202423004.

153 F. Liu, Q. Jiang, Q. Liu, N. Li, Z. Han, C. Liu, Z. Wang, Y. Jiao, J. Sun and B. Ding, Logic-gated plasmonic nanodevices based on DNA-templated assembly, *CCS Chem.*, 2021, **3**, 985–993.

154 M. Zhao, B. Li, H. Zhang and F. Zhang, Activatable fluorescence sensors for *in vivo* bio-detection in the second near-infrared window, *Chem. Sci.*, 2021, **12**, 3448–3459.

155 Z. Ma, S. Tang, W. Shen and H. K. Lee, Advanced applications of DNA hydrogels in fluorescence sensing, *TrAC Trends Anal. Chem.*, 2024, 117907.

156 L. Wang, Y. Zhuang, R. Pan, T. Wang, J. Zhang, D. Wang, C. Liu, W. Shen and S. Tang, Simultaneous targeting and monitoring of free antigen and in-situ membrane antigen in prostate cancer cells via an aggregation-induced emission-based bifunctional probe, *Biosens. Bioelectron.*, 2024, **263**, 116581.

157 C. Song, C. Liu, J. Chen, Z. Ma, S. Tang, R. Pan, X. Suo, Z. Yan, H. K. Lee and W. Shen, Self-generation of distinguishable fluorescent probes *via* a one-pot process for multiple microRNA detection by liquid chromatography, *Anal. Chem.*, 2023, **95**, 4113–4121.

158 Y. Cai, T. Dong, Z. Bian, H. Liu, X. Liu and A. Liu, Metal-organic frameworks based fluorescent sensing: Mechanisms and detection applications, *Coord. Chem. Rev.*, 2025, **529**, 216470.

159 Z. Bian, E. Gomez, M. Gruebele, B. G. Levine, S. Link, A. Mehmood and S. Nie, Bottom-up carbon dots: purification, single-particle dynamics, and electronic structure, *Chem. Sci.*, 2025, **16**, 4195–4212.

160 W. Zhong and L. Shang, Photoswitching the fluorescence of nanoparticles for advanced optical applications, *Chem. Sci.*, 2024, **15**, 6218–6228.

161 X. Zhou, L. Miao, W. Zhou, Y. Chen, Y. Ruan, X. Wang, G. Wang, P. Bao, Q. Qiao and Z. Xu, Enhancing the photostability of red fluorescent proteins through FRET with Si-rhodamine for dynamic super-resolution fluorescence imaging, *Chem. Sci.*, 2025, **16**, 10476–10486.

162 M. Xiao, Q. Zhou, H. Zhang, L. Zhou, J. Ma and C. Yi, Logic gate design using multicolor fluorescent carbon nanodots for smartphone-based information extraction, *ACS Appl. Nano Mater.*, 2021, **4**, 8184–8191.

163 F. Wang, Y. Lan and Y. Zuo, Polysiloxane-based molecular logic gate for dual-channel visualizing mitochondrial pH and sulphite changes during cuproptosis, *Anal. Chem.*, 2023, **95**, 14484–14493.

164 M. Wang, Y. Da and Y. Tian, Fluorescent proteins and genetically encoded biosensors, *Chem. Soc. Rev.*, 2023, **52**, 1189–1214.

165 Z. Chen, R. D. Kibler, A. Hunt, F. Busch, J. Pearl, M. Jia, Z. L. VanAernum, B. I. Wicky, G. Dods and H. Liao, De novo design of protein logic gates, *Science*, 2020, **368**, 78–84.

166 Y. L. Vishweshwaraiah, J. Chen, V. R. Chirasani, E. D. Tabdanov and N. V. Dokholyan, Two-input protein logic gate for computation in living cells, *Nat. Commun.*, 2021, **12**, 6615.

167 Z. Luo, Y. Li, P. Zhang, L. He, Y. Feng, Y. Feng, C. Qian, Y. Tian and Y. Duan, Catalytic hairpin assembly as cascade nucleic acid circuits for fluorescent biosensor: Design, evolution and application, *TrAC Trends Anal. Chem.*, 2022, **151**, 116582.

168 F. Deng, J. Pan, M. Chen, Z. Liu, J. Chen and C. Liu, Integrating CRISPR-Cas12a with catalytic hairpin assembly as a logic gate biosensing platform for the detection of polychlorinated biphenyls in water samples, *Sci. Total Environ.*, 2023, **881**, 163465.

169 J. Pan, F. Deng and J. Chen, A fluorescent biosensor for Cd^{2+} detection in water samples based on Cd^{2+}-fueled wheel DNAzyme walker and its logic gate applications, *Sci. Total Environ.*, 2023, **864**, 161046.

170 L. Liu, L. Ga and J. Ai, Ratiometric fluorescence sensing with logical operation: Theory, design and applications, *Biosens. Bioelectron.*, 2022, **213**, 114456.
171 K. Yang, P. Jia, J. Hou, S. Zhao and L. Wang, An ingenious turn-on ratiometric fluorescence sensor for sensitive and visual detection of tetracyclines, *Food Chem.*, 2022, **396**, 133693.
172 Y. Tian, Y. Mou, W. Zhang, Z. Sun, Y. Yin, L. Han, D. Chen, Y. Guo, X. Sun and F. Li, A fluorescence and colorimetric dual-mode aptasensor for kanamycin detection, *Biosens. Bioelectron.*, 2024, 116911.
173 J. Hou, J. Wang, J. Han, J. Wang, D. Chao, Q. Dong, D. Fan and S. Dong, An intelligent ratiometric fluorescent assay based on MOF nanozyme-mediated tandem catalysis that guided by contrary logic circuit for highly sensitive sarcosine detection and smartphone-based portable sensing application, *Biosens. Bioelectron.*, 2024, **249**, 116035.
174 J. Ge, J. Song and X. Xu, Colorimetric detection of viral RNA fragments based on an integrated logic-operated three-dimensional DNA walker, *Biosens. Bioelectron.*, 2022, **217**, 114714.
175 N. Borah, M. N. Kaka and C. Tamuly, "AND"-logic gate-based colorimetric detection of thiocyanate in milk samples using AgNP-EBF as plasmonic nano sensor, *Food Chem.*, 2023, **425**, 136522.
176 S. Gong, X. Wang, P. Zhou, W. Pan, N. Li and B. Tang, AND logic-gate-based CRISPR/Cas12a biosensing platform for the sensitive colorimetric detection of dual miRNAs, *Anal. Chem.*, 2022, **94**, 15839–15846.
177 H. Wang, M. Li, H. Zhang and L. Yang, A tunable threshold colorimetric DNA logic gate for intuitive assessment of chemical contaminant exceedance, *Anal. Chem.*, 2024, **96**, 11862–11868.
178 J.-H. Choi, J. Lim, M. Shin, S.-H. Paek and J.-W. Choi, CRISPR-Cas12a-based nucleic acid amplification-free DNA biosensor via Au nanoparticle-assisted metal-enhanced fluorescence and colorimetric analysis, *Nano Lett.*, 2020, **21**, 693–699.
179 M. Rong, Y. Huang, X. Zhuang, Y. Ma, H. Xie, Y. Wu and L. Niu, AND logic-gate-based Au@ MnO_2 sensing platform for tetracyclines with fluorescent and colorimetric dual-signal readouts, *Sens. Actuators, B*, 2023, **393**, 134204.
180 H. Han, C. Wang, X. Yang, S. Zheng, X. Cheng, Z. Liu, B. Zhao and R. Xiao, Rapid field determination of SARS-CoV-2 by a colorimetric and fluorescent dual-functional lateral flow immunoassay biosensor, *Sens. Actuators, B*, 2022, **351**, 130897.
181 R. Gao, Y. Lin, Y.-L. Ying, Y.-X. Hu, S.-W. Xu, L.-Q. Ruan, R.-J. Yu, Y.-J. Li, H.-W. Li and L.-F. Cui, Wireless nanopore electrodes for analysis of single entities, *Nat. Protoc.*, 2019, **14**, 2015–2035.
182 Y.-L. Ying, Z. Ding, D. Zhan and Y.-T. Long, Advanced electroanalytical chemistry at nanoelectrodes, *Chem. Sci.*, 2017, **8**, 3338–3348.
183 F. Meng, W. Yu, M. Niu, X. Tian, Y. Miao, X. Li, Y. Zhou, L. Ma, X. Zhang and K. Qian, Ratiometric electrochemical OR gate assay for NSCLC-derived exosomes, *J. Nanobiotechnol.*, 2023, **21**, 104.
184 L. Zhu, L. Yu, J. Ye, M. Yan, Y. Peng, J. Huang and X. Yang, A ratiometric electrochemiluminescence strategy based on two-dimensional nanomaterial-nucleic acid interactions for biosensing and logic gates operation, *Biosens. Bioelectron.*, 2021, **178**, 113022.
185 L.-Y. Yang, J.-L. Huang, Y. Lin, Q.-Q. Cai, Y.-J. Zheng, Y. Wu, J.-Y. Chen and X.-H. Lin, A split-type electrochemical biosensor using enzyme-linked DNA magnetic beads realizes the detection of BCR/ABLp210 fusion gene in clinical samples: Duplex ligation chain reaction coupled with OR logic gate design, *Chem. Eng. J.*, 2024, **479**, 147683.
186 Y. Chen, L. Xu, Q. Xu, Y. Wu, J. Li and H. Li, A waste-free entropy-driven DNA nanomachine for smartly designed photoelectrochemical biosensing of MicroRNA-155, *Biosens. Bioelectron.*, 2022, **215**, 114569.
187 B. Xie, S. Du, H. Gao, J. Zhang, H. Fu and Y. Liao, An electrochemical biosensor equipped with a logic circuit as a smart automaton for two-miRNA pattern detection, *Analyst*, 2024, **149**, 5110–5117.
188 D. Capelli, V. Scognamiglio and R. Montanari, Surface plasmon resonance technology: Recent advances, applications and experimental cases, *TrAC Trends Anal. Chem.*, 2023, **163**, 117079.
189 K. Zhang, M. Luo, H. Rao, H. Liu, R. Qiang, X. Xue, J. Li, X. Lu and Z. Xue, Plasmonic and nanozyme dual-channel-based logic judgment for enhancing gold nanoparticle based colorimetric Hg^{2+} ion sensing performance, *Chem. Commun.*, 2024, **60**, 10005–10008.
190 C. Zhang, Y. Zhou, H. Han, H. Zheng, W. Xu and Z. Wang, Dopamine-triggered hydrogels with high transparency, self-adhesion, and thermoresponse as skinlike sensors, *ACS Nano*, 2021, **15**, 1785–1794.
191 S. Hao, R. Dai, Q. Fu, Y. Wang, X. Zhang, H. li, X. liu and J. Yang, A robust and adhesive hydrogel enables interfacial coupling for continuous temperature monitoring, *Adv. Funct. Mater.*, 2023, **33**, 2302840.
192 L. Wu, Y. Ji, H. Dan, C. R. Bowen and Y. Yang, A multifunctional optical-thermal logic gate sensor array based on ferroelectric $BiFeO_3$ thin films, *InfoMat*, 2023, **5**, e12414.
193 L. Wang, J. Song and C. Yu, Recent progress on mass-sensitive gas sensors for environmental and industrial applications, *Measurement*, 2025, **249**, 117039.
194 L. Shi, Q. Tang, B. Yang, W. Liu, B. Li, C. Yang and Y. Jin, Logic-gates of gas pressure for portable, intelligent and multiple analysis of metal ions, *Anal. Chem.*, 2023, **95**, 5702–5709.
195 Y. Ouyang, X. Li, Y. Du, Y. Zhang, Z. L. Wang and D. Wei, Mechano-driven neuromimetic logic gates established by geometrically asymmetric hydrogel iontronics, *Small*, 2025, **21**, 2409998.
196 P. Cao, Y. Wang, L. Yu, M. Wang, L. Zhao and X. Hou, Dynamic asymmetric mechanical responsive carbon nanotube fiber for ionic logic gate, *Chin. Chem. Lett.*, 2024, **35**, 109421.

197 S. Lee, J. S. Park, H. Woo, Y. K. Yoo, D. Lee, S. Chung, D. S. Yoon, K.-B. Lee and J. H. Lee, Rapid deep learning-assisted predictive diagnostics for point-of-care testing, *Nat. Commun.*, 2024, **15**, 1695.

198 T. Xu, Y. Zhang, S. Li, C. Dai, H. Wei, D. Chen, Y. Zhao, H. Liu, D. Li and P. Chen, Deep learning-enhanced hand-driven microfluidic chip for multiplexed nucleic acid detection based on RPA/CRISPR, *Adv. Sci.*, 2025, 2414918.

199 P. Lu, Y. Zhou, X. Niu, C. Zhan, P. Lang, Y. Zhao and Y. Chen, Deep-learning-assisted microfluidic immunoassay via smartphone-based imaging transcoding system for on-site and multiplexed biosensing, *Nano Lett.*, 2025, **25**, 6803–6812.

200 Y. Li, T. Lucci, M. Villarruel Dujovne, J. K. Jung, D. A. Capdevila and J. B. Lucks, A cell-free biosensor signal amplification circuit with polymerase strand recycling, *Nat. Chem. Biol.*, 2025, 1–10.

201 X. Li, M. Liu, X. Xia, X. Zeng, D. Men, Y. Duan, J. Hou, C. Hou and D. Huo, Deep learning assisted, smartphone based universal Multi-RPA-CRISPR/Cas12a-G4 portable chip for simultaneous detection of CaMV35S and NOS, *Food Control*, 2025, **168**, 110947.

202 J. Li, X. Wu, Y. Li, X. Wang, H. Huang, D. Jian, Y. Shan, Y. Zhang, C. Wu, G. Tan, S. Wang and F. Liu, Amplification-free smartphone-based attomolar HBV detection, *Biosens. Bioelectron.*, 2021, **194**, 113622.

203 Z. Zhao, R. Wang, X. Yang, J. Jia, Q. Zhang, S. Ye, S. Man and L. Ma, Machine learning-assisted, dual-channel CRISPR/Cas12a biosensor-in-microdroplet for amplification-free nucleic acid detection for food authenticity testing, *ACS Nano*, 2024, **18**, 33505–33519.

204 E. Amalfitano and K. Pardee, Logic invades cell-free biosensing, *Nat. Chem. Biol.*, 2022, **18**, 356–358.

205 R. W. Peeling, D. L. Heymann, Y.-Y. Teo and P. J. Garcia, Diagnostics for COVID-19: moving from pandemic response to control, *Lancet*, 2022, **399**, 757–768.

206 K. Qaderi, A. Shamsabadi, A. Haseli, S. G. Ezabadi, L. Asadi, Y. Jesmani, M. Kalhor, B. Jamali, M. Kajbafvala and A. Mohammadi, Changes in screening, diagnosis, management, and outcomes of gestational diabetes during the COVID-19 pandemic: A systematic review, *Heliyon*, 2024, **10**, e31943.

207 H. Zhang, L. Cao, J. Brodsky, I. Gablech, F. Xu, Z. Li, M. Korabecna and P. Neuzil, Quantitative or digital PCR? A comparative analysis for choosing the optimal one for biosensing applications, *TrAC Trends Anal. Chem.*, 2024, **174**, 117676.

208 X. Terzapulo, A. Kassenova and R. Bukasov, Immunoassays: Analytical and clinical performance, challenges, and perspectives of SERS detection in comparison with fluorescent spectroscopic detection, *Int. J. Mol. Sci.*, 2024, **25**, 2080.

209 S. Kim, G. Cho, J. Lee, K. Doshi, S. Gharpure, J. Kim, J. Gwak, J. M. Hardie, M. K. Kanakasabapathy and H. Kandula, Ultrasensitive and long-lasting bioluminescence immunoassay for point-of-care viral antigen detection, *Nat. Biomed. Eng.*, 2025, 1–15.

210 Y. M. Hassan, A. S. Mohamed, Y. M. Hassan and W. M. El-Sayed, Recent developments and future directions in point-of-care next-generation CRISPR-based rapid diagnosis, *Clin. Exp. Med.*, 2025, **25**, 33.

211 H. Satam, K. Joshi, U. Mangrolia, S. Waghoo, G. Zaidi, S. Rawool, R. P. Thakare, S. Banday, A. K. Mishra and G. Das, Next-generation sequencing technology: current trends and advancements, *Biology*, 2023, **12**, 997.

212 W. Engelen, C. Sigl, K. Kadletz, E. M. Willner and H. Dietz, Antigen-triggered logic-gating of DNA nanodevices, *J. Am. Chem. Soc.*, 2021, **143**, 21630–21636.

213 X. Chai, Z. Fan, M.-M. Yu, J. Zhao and L. Li, A redox-activatable DNA nanodevice for spatially-selective, AND-gated imaging of ATP and glutathione in mitochondria, *Nano Lett.*, 2021, **21**, 10047–10053.

214 C. H. Woo, S. Jang, G. Shin, G. Y. Jung and J. W. Lee, Sensitive fluorescence detection of SARS-CoV-2 RNA in clinical samples via one-pot isothermal ligation and transcription, *Nat. Biomed. Eng.*, 2020, **4**, 1168–1179.

215 J. Lim, A. B. Van, K. Koprowski, M. Wester, E. Valera and R. Bashir, Amplification-free, OR-gated CRISPR-Cascade reaction for pathogen detection in blood samples, *Proc. Natl. Acad. Sci. U. S. A.*, 2025, **122**, e2420166122.

216 B. Weng, Y. Wang, Q. Zhang, Y. Jiang, J. Shang, X. Liu and F. Wang, A versatile DNAzyme-amplified protease-sensing platform for accurate diagnosis of SARS-CoV-2 and reliable classification of colorectal cancer, *Angew. Chem., Int. Ed.*, 2025, **64**, e202507241.

217 Q. Yang, M.-J. Dong, J. Xu, Y. Xing, Y. Wang, J. Yang, X. Meng, T. Xie, Y. Li and H. Dong, CRISPR/RNA aptamer system activated by an AND logic gate for biomarker-driven theranostics, *J. Am. Chem. Soc.*, 2024, **147**, 169–180.

218 S. D. Dwivedi, S. D. Yadav, D. Sahu, D. Singh and M. R. Singh, Revolutionizing genetic diagnostics: Innovative techniques for inherited disease detection, *Gene Rep.*, 2024, 101963.

219 M. Li, F. Yin, L. Song, X. Mao, F. Li, C. Fan, X. Zuo and Q. Xia, Nucleic acid tests for clinical translation, *Chem. Rev.*, 2021, **121**, 10469–10558.

220 C. Emanuelson, A. Bardhan and A. Deiters, DNA logic gates for small molecule activation circuits in cells, *ACS Synth. Biol.*, 2024, **13**, 538–545.

221 M. Wen, Z. Huang, Y. Yin, Y. Wang, M. Wang, X. Huang, T. Chen, G. Ke, M. Chen and X.-B. Zhang, Dual mature microRNA-responsive logic biosensing platform based on CRISPR/Cas12a and DNA nanocage, *Talanta*, 2025, **283**, 127078.

222 L. Shi, Q. Tang, B. Yang, W. Liu, B. Li, C. Yang and Y. Jin, Dual-mode logic gate for intelligent and portable detection of microRNA based on gas pressure and lateral flow assay, *Anal. Chem.*, 2023, **95**, 6090–6097.

223 W. Peng, T. Zhou, L. Hu, V. Vankann, T. Bohn, T. Bopp, S. L. Kuan and T. Weil, Autonomous activation of a gated chemiluminescent photosensitizer enables targeted photodynamic therapy in tumor cells, *J. Am. Chem. Soc.*, 2025, **147**, 27822–27834.

224 A. Escudero, F. J. Hicke, E. Lucena-Sánchez, S. Pradana-López, J. J. Esteve-Moreno, V. Sanz-Álvarez, I. Garrido-Cano, S. Torres-Ruiz, J. M. Cejalvo, A. García-Fernández, P. Díez and R. Martínez-Máñez, Glucose-fueled gated nanomotors: Enhancing *in vivo* anticancer efficacy via deep drug penetration into tumors, *ACS Nano*, 2025, **19**, 20932–20955.

225 Y. Shen, S. j. Jin, Y. c. Chen, W. h. Liu, Y. m. Li, W. y. Zhao, Y. c. Xu, S. q. Chen and W. b. Zhao, Improving the tumor selectivity of T cell engagers by logic-gated dual tumor-targeting, *Pharmacol. Res.*, 2023, **192**, 106781.

226 Y. Sima, L. Ai, L. Wang, P. Zhang, Q. Zhang, S. Wu, S. Xie, Z. Zhao and W. Tan, A DNA molecular logic circuit for precise tumor identification, *Nano Lett.*, 2024, **24**, 12070–12079.

227 Q. Chao, Y. Zhang, Q. Li, L. Jiao, X. Sun, X. Chen, L. Zhu, Q. Yang, C. Shang and R.-M. Kong, Compute-and-release logic-gated DNA cascade circuit for accurate cancer cell imaging, *Anal. Chem.*, 2023, **95**, 7723–7734.

228 Y. Pan, X. Luan, F. Zeng, X. Wang, S. Qin, Q. Lu, G. He, Y. Gao, X. Sun and X. Han, Logic-gated tumor-microenvironment nanoamplifier enables targeted delivery of CRISPR/Cas9 for multimodal cancer therapy, *Acta Pharm. Sin. B*, 2024, **14**, 795–807.

229 M. Hong, J. D. Clubb and Y. Y. Chen, Engineering CAR-T cells for next-generation cancer therapy, *Cancer Cell*, 2020, **38**, 473–488.

230 A. M. Tousley, M. C. Rotiroti, L. Labanieh, L. W. Rysavy, W.-J. Kim, C. Lareau, E. Sotillo, E. W. Weber, S. P. Rietberg and G. N. Dalton, Co-opting signalling molecules enables logic-gated control of CAR T cells, *Nature*, 2023, **615**, 507–516.

231 O. Nolan-Stevaux and R. Smith, Logic-gated and contextual control of immunotherapy for solid tumors: contrasting multi-specific T cell engagers and CAR-T cell therapies, *Front. Immunol.*, 2024, **15**, 1490911.

232 M. Hamieh, J. Mansilla-Soto, I. Rivière and M. Sadelain, Programming CAR T cell tumor recognition: tuned antigen sensing and logic gating, *Cancer Discov.*, 2023, **13**, 829–843.

233 C. Zhang, Y.-Q. Min, H. Xue, H. Zhang, K. Liu, Y. Tian, Z. Yang, Z. Zhao, H. Yang and C. Shan, Host protein ARF1 is a proviral factor for SARS-CoV-2 and a candidate broad-spectrum therapeutic target, *Nat. Commun.*, 2025, **16**, 6326.

234 C. Jiang, X. Mu, S. Liu, Z. Liu, B. Liu, B. Du and Z. Tong, A study of the detection of SARS-CoV-2 by the use of electrochemiluminescent biosensor based on asymmetric polymerase chain reaction amplification strategy, *IEEE Sens. J.*, 2022, **23**, 8094–8100.

235 Q. Zhang, Z. Feng, Y. Hao, L. Wei, A. Wang, Z. Han, M. Tian, S. Sun, X. g. Li and T. Xue, Dynamic changes of ORF1ab and N gene Ct values in COVID-19 omicron inpatients of different age groups-Beijing municipality, China, November-December 2022, *China CDC Weekly*, 2023, **5**, 180.

236 M. M. H. Sarkar, S. R. Naser, S. F. Chowdhury, M. S. Khan, M. A. Habib, S. Akter, T. A. Banu, B. Goswami, I. Jahan and M. R. Nayem, M gene targeted qRT-PCR approach for SARS-CoV-2 virus detection, *Sci. Rep.*, 2023, **13**, 16659.

237 T. Chen, P. Liu, H. Wang, Y. Su, S. Li, S. Ma, X. Xu, J. Wen and Z. Zou, Dumbbell-type triplex molecular switch-based logic molecular assays of SARS-CoV-2, *Sens. Actuators, B*, 2022, **371**, 132579.

238 S. Bhadra, T. E. Riedel, S. Lakhotia, N. D. Tran and A. D. Ellington, High-surety isothermal amplification and detection of SARS-CoV-2, *mSphere*, 2021, **6**, e00911–e00920.

239 Y. Wu, R. Jin, Y. Chang and M. Liu, A high-fidelity DNAzyme-assisted CRISPR/Cas13a system with single-nucleotide resolved specificity, *Chem. Sci.*, 2024, **15**, 6934–6942.

240 F. Deng, J. Pan, Z. Liu, L. Zeng and J. Chen, Programmable DNA biocomputing circuits for rapid and intelligent screening of SARS-CoV-2 variants, *Biosens. Bioelectron.*, 2023, **223**, 115025.

241 Y. Huang, Q. Wu, J. Zhang, Y. Zhang, S. Cen, C. Yang and Y. Song, Microfluidic enrichment of intact SARS-CoV-2 viral particles by stoichiometric balanced DNA computation, *ACS Nano*, 2023, **17**, 21973–21983.

242 H. Li, H. Lu, Y. Tang, H. Wang, Y. Xiao and B. Li, A rebuilding-free nucleic acid detection strategy enables ultrasensitive genotyping, N-in-1 logic screening and accurate multiplex assay of dangerous pathogens, *Angew. Chem., Int. Ed.*, 2022, **61**, e202209496.

243 J. Chen, T. Liu, Y. Zhang, M. Duan, Z. Yang, M. Chen, Y. Wang, L. Zheng, S. Zhuang and D. Zhang, One-step time-resolved cascade logic gate microfluidic chip for home testing of SARS-CoV-2 and flu B, *Biosens. Bioelectron.*, 2024, **263**, 116564.

244 P. Sen, Z. Zhang, S. Sakib, J. Gu, W. Li, B. R. Adhikari, A. Motsenyat, J. L'Heureux-Hache, J. C. Ang and G. Panesar, High-precision viral detection using electrochemical kinetic profiling of aptamer-antigen recognition in clinical samples and machine learning, *Angew. Chem., Int. Ed.*, 2024, **63**, e202400413.

245 Z. Jiao, J. Yang, X. Long, Y. Lu, Z. Guo, Y. Peng, X. Huang, Y. Yin, C. Song and P. Zhang, CRISPR/Cas12a-assisted visual logic-gate detection of pathogenic microorganisms based on water-soluble DNA-binding AIEgens, *Front. Chem.*, 2022, **9**, 801972.

246 F. Petronella, D. De Biase, C. Santini, A. Avitabile, M. L. Sforza, F. Zaccagnini, A. d'Alessandro and L. De Sio, Logic-OR gate gold nanorod-based plasmonic biosensor for multipathogen detection and photothermal disinfection, *Mater. Adv.*, 2025, **6**, 1107–1118.

247 J. Tian, D. Shi, Y. Zhang, X. Li, X. Li, H. Teng, T. D. James, J. Li and Y. Guo, Stress response decay with aging visualized using a dual-channel logic-based fluorescent probe, *Chem. Sci.*, 2021, **12**, 13483–13491.

248 H. Nan, M. Cai, S. Kuang and Z. Nie, Monitoring of cell membrane microenvironment based on DNA nanodevices, *Chem. Res. Chin. Univ.*, 2024, **40**, 255–267.

249 S. Chen, Z. Xu, W. Yang, X. Lin, J. Li, J. Li and H. Yang, Logic-gate-actuated DNA-controlled receptor assembly for the programmable modulation of cellular signal

transduction, *Angew. Chem., Int. Ed.*, 2019, **58**, 18186–18190.

250 M. Yu, J. Shang, C. Xie, Y. Jiang, Y. Wang, X. Liu and F. Wang, An integrated sequential-activated DNA circuit for reliable imaging of intracellular miRNA and remote control of cellular function, *Adv. Funct. Mater.*, 2025, 2508992.

251 H. Gong, Q. Dai and P. Peng, Cell-membrane-anchored DNA logic-gated nanoassemblies for in situ extracellular bioimaging, *ACS Appl. Mater. Interfaces*, 2022, **14**, 43026–43034.

252 C. Dong, J. Xiong, Y. Wang, J. Liang, C. Yan, H. Lv, J. Zhang, C. Song and L. Wang, DNA walker-powered SERS logic aptasensors for accurate imaging and identification of tumor cells, *Sens. Actuators, B*, 2024, **401**, 134922.

253 Y. Fang, Y. Zhang, S. Bi, B. Peng, C. Wang, H. Ju and Y. Liu, Securing LYTAC with logic-identification system for cancer cell-selective membrane protein degradation, *Small*, 2024, **20**, 2310039.

254 J. Sun, X. Xiong, W. Lai, Z. Wu, H. Wang, L. Yang, N. Xue, Q. Yao, G. Song and Y. Zhao, Implementing complex nucleic acid circuits in living cells, *Sci. Adv.*, 2025, **11**, eadv6512.

255 K. Li, X. Yang, J. Ma, C. Su, M. Wang and S. Ye, DNA nanolock-based logic gate-directed reciprocal feedback for stepwise cell typing and combination treatment, *Anal. Chem.*, 2024, **96**, 19687–19694.

256 J. Wang, Y. Wang, J. Zhu, X. Zhu, T. Su, G. Wu, L. Fan, J. Li, Y. Liu and F. Gao, Endogenous enzyme-activated AND-gate DNA nanomachines for intracellular miRNA detection and cell-selective imaging, *Talanta*, 2025, **283**, 127087.

257 J. Yu, Q. Liu, L. Qi, Q. Fang, X. Shang, X. Zhang and Y. Du, Fluorophore and nanozyme-functionalized DNA walking: A dual-mode DNA logic biocomputing platform for microRNA sensing in clinical samples, *Biosens. Bioelectron.*, 2024, **252**, 116137.

258 J. Zhang and Y. Lu, Biocomputing for portable, resettable, and quantitative point-of-care diagnostics: Making the glucose meter a logic-gate responsive device for measuring many clinically relevant targets, *Angew. Chem., Int. Ed.*, 2018, **57**, 9702–9706.

259 T. Tu, S. Huan, X. Feng, G. Ke, L. Li and X. B. Zhang, Spatial confinement of a dual activatable DNAzyme sensor in the cavity of a DNA nanocage for logic-gated molecular imaging, *Angew. Chem., Int. Ed.*, 2025, **64**, e202424684.

260 L. Wei, Z. Wang, Y. She and H. Fu, CRISPR/Cas multiplexed biosensing: advances, challenges, and perspectives, *Anal. Chem.*, 2025, **97**, 11943–11958.

261 H. Qin, J. Zhou, A. Pang, L. Huang, Z. Liu and Y. Zheng, Microbial dynamic regulatory tools: Design, applications, and prospects, *ACS Synth. Biol.*, 2025, **14**, 2418–2432.

262 R. Yue, M. Chen and N. Ma, Dual microRNA-triggered drug release system for combined chemotherapy and gene therapy with logic operation, *ACS Appl. Mater. Interfaces*, 2020, **12**, 32493–32502.

263 Y. Pan, X. Luan, F. Zeng, X. Wang, S. Qin, Q. Lu, G. He, Y. Gao, X. Sun, X. Han, B. He and Y. Song, Logic-gated tumor-microenvironment nanoamplifier enables targeted delivery of CRISPR/Cas9 for multimodal cancer therapy, *Acta Pharm. Sin. B*, 2024, **14**, 795–807.

264 B. Wang, R. I. Kitney, N. Joly and M. Buck, Engineering modular and orthogonal genetic logic gates for robust digital-like synthetic biology, *Nat. Commun.*, 2011, **2**, 508.

265 Y. Gao, L. Wang and B. Wang, Customizing cellular signal processing by synthetic multi-level regulatory circuits, *Nat. Commun.*, 2023, **14**, 8415.

266 D. J. Chinchilla-Cárdenas, J. S. Cruz-Méndez, J. M. Petano-Duque, R. O. García, L. R. Castro, M. J. Lobo-Castañón and G. O. Cancino-Escalante, Current developments of SELEX technologies and prospects in the aptamer selection with clinical applications, *J. Genet. Eng. Biotechnol.*, 2024, **22**, 100400.

267 R. Ghosh, G. M. Hopping, J. W. Lu, D. W. Hollyfield and D. W. Flaherty, Alkene epoxidation and oxygen evolution reactions compete for reactive surface oxygen atoms on gold anodes, *J. Am. Chem. Soc.*, 2025, **147**, 1482–1496.

268 Y. Wang, K. Nguyen, R. C. Spitale and J. C. Chaput, A biologically stable DNAzyme that efficiently silences gene expression in cells, *Nat. Chem.*, 2021, **13**, 319–326.

269 J. Zhou, L. Mei, M. Yu, X. Ma, D. Hou, Z. Yin, X. Liu, Y. Ding, K. Yang, R. Xiao, X. Yuan, Y. Weng, M. Long, T. Hu, J. Hou, Y. Xu, L. Tao, S. Mei, H. Shen, Y. Yalikun, F. Zhou, L. Wang, D. Wang, S. Liu and C. Lei, Imaging flow cytometry with a real-time throughput beyond 1,000,000 events per second, *Light Sci. Appl.*, 2025, **14**, 76.

270 H. Zhang, J. Vandesompele, K. Braeckmans, S. C. De Smedt and K. Remaut, Nucleic acid degradation as barrier to gene delivery: a guide to understand and overcome nuclease activity, *Chem. Soc. Rev.*, 2024, **53**, 317–360.

271 S. Chatterjee, E. Kon, P. Sharma and D. Peer, Endosomal escape: A bottleneck for LNP-mediated therapeutics, *Proc. Natl. Acad. Sci. U. S. A.*, 2024, **121**, e2307800120.

272 S. Omo-Lamai, Y. Wang, M. N. Patel, A. Milosavljevic, D. Zuschlag, S. Poddar, J. Wu, L. Wang, F. Dong, C. Espy, A. Majumder, E.-O. Essien, M. Shen, B. Channer, T. E. Papp, M. Tobin, R. Maheshwari, S. Jeong, S. Patel, A. Shah, S. Murali, L. S. Chase, M. E. Zamora, M. L. Arral, O. A. Marcos-Contreras, J. W. Myerson, C. A. Hunter, D. Discher, P. J. Gaskill, A. Tsourkas, V. R. Muzykantov, I. Brodsky, S. Shin, K. A. Whitehead, H. Parhiz, J. Katzen, J. J. Miner, D. Trauner and J. S. Brenner, Limiting endosomal damage sensing reduces inflammation triggered by lipid nanoparticle endosomal escape, *Nat. Nanotechnol.*, 2025, **20**, 1285–1297.

273 J. Liu and Q. Zhang, DNA logic circuit based on a toehold independent strand displacement reaction network, *Nano Lett.*, 2025, **25**, 3464–3470.