Biosensors based on DNA logic gates

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Abstract
Biosensor is a device that responds to a particular target in a selective way by incorporation of biological recognition as sensing unit. For practical biomedical applications, a digital output (a qualitative YES/NO answer) is highly demanded for certain end-user or point-of-care applications. Boolean logic, which can be applied to any type of information expressed as 0 (NO) and 1 (YES), is widely employed to achieve such qualitative analysis. Over the past decade, owing to DNA's advantages of stability, accessibility, and manipulability, significant research efforts have been focused on the design and application of DNA logic gates (DLG)-based biosensors capable of implementing logic-gated biomedical functions. This review summarizes the existed representative examples and the advanced developments of DLG biosensors, and discusses the limitations and the future directions on the development of novel nanosensors based on DNA logic operations for realizing highly efficient diagnosis.

KEYWORDS
biosensor, Boolean logic, DNA logic gates, nucleic acids

1 | INTRODUCTION

Biosensors are analytical tools that can convert analyte recognition events into readily detectable readout signals, and have been developed for detection of many different analytes, such as ions, small molecules, proteins, enzymes, and cells.1 Relying on various recognition events, biosensors usually function in a similar manner, that the output signal is proportional to the analyte concentration.2 The sensing performance of biosensors is generally characterized by sensitivity and selectivity, where the sensitivity can be characterized by the dynamic concentration range and limit of detection of analytes while selectivity is evaluated by the influence of various interfering species.3 Typically, biosensors can provide quantitative information on the presence of analytes.4
SCHEME 1 Biosensors based on DNA logic gates (DLG). DLG biosensors generally function through the following procedure: various targets are recognized as inputs, and then trigger DNA logic operation based on strand displacement reactions or conformational change, which consequently generate outputs detected by recognizable readouts.

However, for practical biomedical applications, it is challenging to draw quantitative conclusions based on sensing results of multiple analyte species, whereas a qualitative but rapid YES/NO answer is highly demanded for certain end-user or point-of-care applications. Such analysis can be readily performed using Boolean logic, which in practice can be applied to any type of information expressed as 0 and 1. The presence of a specific target is specified as the Boolean TRUE or “1” value, while the absence is denoted as the Boolean FALSE or “0” value.

Nucleic acids are promising material to construct molecular logic gates. Due to strict base-pairing rules, a series of strand reactions has been designed such as branch migration, toehold reaction, which can be employed for logic computation. In addition, nucleic acids can be easily modified with different molecules or moieties, such as fluorescence molecules, metal nanoparticles, enzymes, and antibodies. More importantly, they can capture certain targets, such as small molecules, proteins, and even the whole cell, in highly specific manners as aptamers.

Over the past decade, significant research efforts have been focused on the design and application of DNA-based biosensors capable of implementing biomedical functions, such as targeting, sensing, imaging, and therapy. Recently, to achieve rapid YES/NO answer, various DNA-based biosensors have been coupled with logic-gated functions. In this review, we focus on biosensors based on DNA logic gates (DLG).

For DLG biosensors, logic calculations are generally obtained by a three-step procedure (Scheme 1), as follows: (a) targets are recognized as inputs by the biosensor, (b) strand displacement reactions or conformational change occur, and (c) outputs are generated with a recognizable readout. To recognize output signals, multi-step procedures such as fluorescent labeling, amplification, sequencing, or imaging are commonly required. Up to date, various basic logic gates have been realized with output signals detected by different instrumentation techniques, including fluorescence, luminescence, electrochemistry, and colorimetry. Here, we sort these highly diverse DLG biosensors into three groups briefly according to their operational environment, e.g., solution, interfaces, and cellular environment. By presenting a number of representative examples, we aim to facilitate a brief overview and comparison of current DLG biosensors, focusing on parameters such as the rational design, inputs and outputs, logic gating operation, outputs readout, and instrumentation. In the end, we discuss current challenges and future potential for DLG biosensors.

2 | DLG-BASED BIOSENSORS IN SOLUTION

Solution is probably the mostly and best studied environment for operation of DLG biosensors, where inputs, DLG, and outputs are freely diffusive depending on environmental temperatures. The diffusion-based kinetics is critical for the speed of logic operation, and the global diffusion of all components affects the logic operation efficiency and complexity.

Based on Mg$^{2+}$-dependent DNAzyme and peroxidase-mimicking G-quadruplex/hemin hybrids, Chen and colleagues constructed a label-free and enzyme-free
sensing platform capable of a universal set of two-input elementary logic gates (OR, AND, NOR, NAND, INHIBIT, IMPLICATION, XOR, and XNOR)\textsuperscript{26} (Table 1, Entry 1). In the presence of appropriate input DNA, active DNAzyme structures were assembled, which consequently cleaved a ribonucleobase (rA)-containing DNA substrate in the presence of Mg\textsuperscript{2+} to release the caged G-quadruplex sequence. Upon incubation with hemin, the G-quadruplex DNAzyme catalyzed the oxidation of 3,3',5,5'-tetramethylbenzidine by H\textsubscript{2}O\textsubscript{2} to generate the change in solution color from colorless to blue, which is readily distinguished by the naked eye. By introducing dynamic sequences in one or more edges of the DNA tetrahedra, e.g., i-motif, ATP aptamer, T-rich mercury-specific oligonucleotide, or hairpin structures, Fan’s group constructed DLG nanosensors that are responsive to H\textsuperscript{+}, ATP, Pb\textsuperscript{2+}, and DNA, which were capable of AND, OR, XOR, and INH logic gate operation\textsuperscript{27} (Figure 1A and Table 1, Entry 2). By attaching a Forster resonance energy transfer pair on one side of the DNA tetrahedra, the target-induced configuration changes of the framework nucleic acid (FNA) nanostructures were translated into variation of the observed fluorescense intensity.

Kawano’s group constructed a label-free signal-amplified AND gate device with DNA as the input and RNA as the output, by using bacteriophage T7 RNA polymerase (T7RP) to integrate amplification and transcription functions into a microdroplet system\textsuperscript{28} (Table 1, Entry 3). The output RNA molecules were electrically detected using α-hemolysin (αHL) nanopores with single-molecule translocation. Based on this work, the same group realized rapid pattern recognition of miRNA-20a and miRNA-17-5p, by discrimination of blocking duration of resulted four-way junction structures captured in the nanopore\textsuperscript{29} (Figure 1B and Table 1, Entry 4). Smartphone can also be used to detect the output of label-free DLG biosensors. Chang et al developed peptide nucleic acid (PNA) sensor composed of a semisynthetic luciferase (H-Luc-PNA conjugate) that is switched on by a strand-displacement reaction. The simple mixing assay enabled sensitive AND-gate detection of microRNA sequences by smartphone imaging of bioluminescent readout\textsuperscript{30} (Table 1, Entry 5).


**TABLE 1** Representative examples of DNA logic gates (DLG)-based biosensors

| Inputs          | Major components                                                                 | Gate function | Operation environment | Outputs                                      | Readout signal                                      | Instrumentation                          | Ref  |
|-----------------|----------------------------------------------------------------------------------|---------------|-----------------------|----------------------------------------------|-----------------------------------------------------|-------------------------------------------|------|
| 1 DNA           | Mg$^{2+}$-dependent DNAzyme, caged G-quadruplex                                | OR, AND, NOR, NAND, INHIBIT, IMPLICATION, XOR, XNOR | Aqueous solution in test tube | Release of G-quadruplex sequence | Blue color of oxidized 3, 3′, 5, 5′-tetramethylbenzidine (TMB) | Naked eye | 26   |
| 2 H$^+$, Hg$^{2+}$, ATP, DNA | Tetrahedral DNA nanostructures containing i-motif, ATP aptamer, and/or T-rich mercury-specific oligonucleotide | INH, XOR, OR, AND | Aqueous solution in test tube | Configuration switch of DNA tetrahedron | Fluorescence change | Fluorescence spectrophotometer | 27   |
| 3 DNA           | T7 RNA polymerase (T7RP)                                                        | AND           | Microdroplets          | Amplification of RNA                        | Current trace                                        | α-hemolysin (αHL) nanopore                | 28   |
| 4 microRNA      | DNA                                                                              | AND           | Microdroplets          | Formation of a four-way junction (4WJ) structure | Current trace                                        | α-hemolysin (αHL) nanopore                | 29   |
| 5 microRNA      | Halo-Tag-–N-Luc chimera conjugated with PNA                                      | AND           | Aqueous solution in test tube | Release of N-Luc inhibitor                   | Bioluminescence                                    | Smartphone                               | 30   |
| 6 Ag$^+$ and Hg$^{2+}$ | DNA capped CdSe/ZnS QDs                                                        | AND, OR       | Surface of CdSe/ZnS QDs | Formation of Hg$^{2+}$–thymine or Ag$^{+}$–cytosine complexes | Fluorescence                                      | Fluorescence spectrophotometer           | 35   |
| 7 ATP and thrombin | Fluorophore-labeled ATP and thrombin binding aptamers, GO                      | OR, INHIBIT   | Surface of GO          | Release of fluorophore-labeled aptamers from GO surface | Fluorescence                                      | Fluorescence spectrophotometer           | 36   |
| 8 microRNA      | DNA origami, biotinylated ssDNA                                               | YES, AND      | Surface of DNA origami | Hybridization of biotinylated ssDNA on DNA origami | Nanoscale symbols of Streptavidin on DNA origami | Atomic force microscope                  | 37   |
| 9 microRNA      | Y-shaped DNA structure, DNA modified AuNPs                                      | AND           | Surface of AuNPs       | Release of DNA from AuNPs                    | Aggregation of AuNPs                                | UV–vis absorption spectrophotometer       | 38   |

(Continues)
# Table 1 (Continued)

| Inputs | DNA logic gates | Output readout | Readout signal | Instrumentation | Ref |
|--------|-----------------|----------------|----------------|-----------------|-----|
| 10     | Thrombin, AuNPs, brilliant cresyl blue | Thrombin-binding aptamer | AND, NOT, INH | Surface of gold electrode | Binding of Thrombin to its aptamer | Electrical signals | Electrochemical workstation, a gold working electrode, a platinum auxiliary electrode, and a Ag/AgCl reference electrode |
| 11     | Cell membrane receptors | Y or X shaped DNA structures containing aptamers Sgc8c, Sgc4f and TC01, chlorine e6 conjugated oligonucleotide | AND, INH | Cell surface | Release of ssDNA from Y or X shaped DNA structures | Fluorescence on cell membrane, photodynamic therapy effect | Flow cytometry, Confocal laser scanning microscope |
| 12     | Cell membrane receptors | DNA triangular prism attached by two aptamers sgc8c and sgc4f | AND | Cell surface | Release of ssDNA from DNA triangular prism | Fluorescence on cell membrane | Flow cytometer, confocal laser scanning microscope |
| 13     | Extracellular H+ and K+ | Two cholesterol labeled tetrahedral DNA nanostructures with different branched vertexes attached by AS1411 and i-motif, respectively | AND | Cell surface | Dimeric assembly of DNA tetrahedron and AS1411 release | FRET on cell membrane | Confocal laser scanning microscope |
| 14     | Synthetic miR-21 or miR-122 or both | DNA duplex | AND | In living cells (transfection needed) | Release of fluorophore or quencher modified ssDNA | Intracellular fluorescence | Fluorescence microscope |
| 15     | Native mRNA | DNA or RNA | OR, AND | In living cells (transfection needed) | Occurrence of four-way strand exchange reactions | Intracellular fluorescence | Flow cytometer, confocal laser scanning microscope |
| 16     | Intratracellular pH and ATP | DNA triangular prism incorporated with i-motif and ATP aptamer | AND | In living cells | Configuration switch of DNA triangular prism | Intracellular FRET signal | Confocal laser scanning microscope |
**3 | DLG BIOSENSORS AT INTERFACES**

The interfaces, in most cases solid–liquid interfaces, provide anti-interference for DNA logic operations through separation and elimination of invalid inputs and verbose outputs in solution, and thus introduce significant potential for enhancing logic operation complexity. The most widely employed interfaces include the surfaces of metal or inorganic nanoparticles, two-dimensional layered nanocomposites, electrodes, DNA origami, microfluidic channels, and so on.

Based on the specific quenching of the quantum dots (QDs) by the ions via an electron-transfer-quenching path, Willner’s group constructed AND and OR gates by using nucleic acid functionalized CdSe/ZnS QDs, realizing the simultaneous selective analysis of Hg2⁺ and Ag⁺ by fluorescence change (Table 1, Entry 6). By absorbing 6-carboxyfluorescein (FAM)-labeled adenosine triphosphate binding aptamer (ABA) and FAM-labeled thrombin binding aptamer (TBA) onto graphene oxide (GO), Dong and colleagues constructed a GO/aptamer complex capable of enzyme-free OR and INHIBIT logic operations with multiple targets as inputs. The observed fluorescence outputs changed according to different input combinations (Table 1, Entry 7). Song’s group realized YES and AND logic gates on rectangular DNA origami for miRNA analysis, with microRNA-21 and microRNA-195 as the inputs and two different nanoscale symbols, “+” (positive) or “−” (negative), as the outputs. These logic nanosystems were label-free and purely composed of DNA. The output symbols on DNA origami could be visually observed with atomic force microscopy (Table 1, Entry 8). Combining a duplex Y-shaped structure formed with three DNA strands and hybridization chain reaction, Miao and colleagues developed a triple-input DNA AND logic gate to evaluate the concentration of initial miRNA inputs with the non-cross-linking aggregation of AuNPs as the output readout (Table 1, Entry 9). Li’s group reported a Boolean logic tree on gold electrode, which serves as a dual-signal electrochemical aptasensor system for amplification detection of thrombin (Figure 1C and Table 1, Entry 10).

**4 | DLG BIOSENSORS IN CELLULAR ENVIRONMENT**

**4.1 | DLG biosensors at cell membrane**

Complex components on cell membrane surface play essential biological roles in cellular events, such as cell-cell communication, cell growth, proliferation, and death. Various DLG biosensors capable of implementing cell membrane analysis to distinguish multiple markers between diseased and normal cells have been reported.

Based on the fast development of cell-Systematic Evolution of Ligands by EXponential enrichment technology, aptamers hold promise to differentiate the expression patterns of complicated membrane biomarkers. Combining the structure-switching properties of DNA aptamers with toehold-mediated strand displacement reactions, Tan and colleagues designed DNA-based devices capable of logic-based analysis of multiple cancer cell-surface markers, in particular the AND gate (Table 1, Entry 11). By employing two aptamers of membrane biomarkers on one 3D DNA scaffold, that is, sgc8c (targeting tyrosine-protein kinase-like 7) and sgc4f (unidentified target), the same group engineered a DNA-logic gate triangular prism for cell-surface recognition and Boolean logic operation (Table 1, Entry 12). Compared to freely dispersed dsDNA-based circuits, this 3D DLG strategy incorporated all logic units into one scaffold, and showed higher identification performance by reporting a “ON” signal when the specific cell type is presented.

In addition to recognize membrane biomarkers, biosensors on cell surface can also be designed to logically respond to extracellular microenvironment, such as pH values, ions, and biomolecules. As a recent example, Lu and colleagues integrate a cell-surface-anchored AND-gated logic sensor based on in situ dimeric assembly of tetrahedral DNA nanostructures (TDNs) on cell surface triggered by extracellular H⁺ and K⁺ (Figure 1d and Table 1, Entry 13). The sensor consists of two TDNs with branched vertex for tethering pH responsive i-motif and anticancer aptamer AS1411, respectively, which are attached on cell membrane by cholesterol anchorage. Interestingly, this FNA nanosensor also enabled more efficient AS1411 internalization by cancer cells in response to extracellular stimuli.

**4.2 | DLG biosensors in living cells**

DLG biosensors have been widely utilized to analyze multiple molecular markers in living cells, such as miRNA, metal ions, and pH values, and the generated outputs enable applications beyond intracellular detection. They have long been motivated by the aim to build “smart therapeutics,” but the cellular environment is significantly different from the cell-free conditions. The logic operation of DLG biosensors may suffer from delivery issues, serious degradation, and immune recognition. To realize such application in living cells, it is necessary to carefully address the following three issues.
Delivery

In most cases, DLG biosensors used for intracellular detection are chemically synthesized and transiently delivered to mammalian cells, rather than genetically encoded and expressed in cells. Variation of delivery strategies may result in differences of DLG-based sensors in uptake time, subcellular distribution, and cell viability. The most commonly employed delivery strategy is the usage of transfection reagents, which could deliver large amounts of DNA devices to cells, but it suffers from endosome enclosing, and thus the probes may not reach the cytoplasm. In contrast, microinjection delivers the probes to the cytoplasm or nucleus directly, but is limited to a small number of cells. Up to date, researchers have developed series of new methods to efficiently deliver DLC-based sensors into living cells, such as nanoparticle-based delivery systems.

Cellular molecular crowding

In reaction buffers, the environmental conditions, such as concentration of all components and pH value of solution, could be precisely controlled, so the kinetics of reaction is monitored with high resolution. However, cells are packed with proteins, small molecules, nucleic acids, and other biomolecules, which would adversely affect the performance of DLG and consequently result in false signals. It has been demonstrated that the diffusion coefficient of DNA probes is 5-100 times smaller in the cytoplasm than in reaction buffers, which indicates significant difference between the DNA hybridization process in complex cellular environment and cell-free conditions. Therefore, a systematic understanding of how to adapt DLG biosensors from cell-free settings to the intracellular environment is highly demanded, but extremely challenging. To properly control interactions of DNA logic nanodevices with cells and consequently the logic operation performance, the case-by-case optimization of design parameters and delivery method is required.

Immune recognition

It has been well established that exogenously DNA or RNA probes would trigger immune responses through Toll-like receptors (TLR), such as single-strand RNAs responsive TLR8 and TLR7, and double-strand RNAs responsive TLR3. To avoid such immune stimulation, a commonly used method is to employ artificial carrier with excellent biocompatibility, such as viral capsid proteins. Meanwhile, activation of immune responses by DNA logic nanodevices also holds promise for therapeutic applications where immune stimulation may be desirable.

As one of the pioneering works, Hemphill and Deiters engineered oligonucleotide AND gates for the cell-specific identification of endogenous miRNAs in living mamalian cells (Table 1, Entry 14). The gate devices were directly transfected into cells together with input strands, and their logic gate function was specifically activated through the addition of either synthetic miR-21 or miR-122 or both miRNAs, with intracellular fluorescence as the indication of outputs. Groves et al reported novel DLG devices that can directly interact with native mRNAs (Table 1, Entry 15). To minimize crosstalk with other nucleic acids in cellular environments, they focused on the four-way strand exchange mechanism and optimized the device design by systematically varying the chemical composition and delivery method. Among various transfection reagents tested, Lipofectamine 2000 (L2K) efficiently prevented the interaction between the input and reporter before entering the cells. They demonstrated AND and OR logic gates in cells and found that functional siRNA could be activated through strand exchange. By combining pH sensitive i-motif and ATP-binding aptamer (ABA) on the scaffold of a DNA triangular prism, Lu and colleagues recently developed an FNA nanodevice responding to the changes of lysosomal pH and ATP levels modulated by external stimuli chloroquine and oligomycin (Figure 1E and Table 1, Entry 16). This FNA nanodevice could easily enter cells via the caveolae-mediated endocytosis pathway and remain intact inside cells for over 8 hours. The output is recorded as fluorescence resonance energy transfer signal by confocal imaging.

5 CURRENT CHALLENGES AND FUTURE PERSPECTIVES

In last decade, substantial advances toward the development of DLG biosensors have offered enormous opportunities and advantages for bioanalysis, although important challenges and hurdles still remain. Here we discuss a few important issues.

First, the logic operation of reported DLG biosensors occurred mainly in simple artificial environments, e.g., buffer solutions, and should be validated in complex biofluids such as saliva, urine, serum, and blood, where stability of DLG and complex interference inputs may limit the sensing performance. One possible solution to the problem of instability is to employ artificial nucleotides for the preparation of DLG.
nanostructured rigid scaffolds could greatly improve the biostability of DLG biosensors in complex biological systems, as well as the sensor performance. Some scaffolds, such as AuNPs and FNAs, also serve as efficient carrier to deliver DLG into living cells. More importantly, rational designs would contribute to the DNA logic operations in complex biofluids. For example, based on DNA strand displacement cascades, Rudchenko et al. developed antibody-directed DNA devices that can analyze lymphocytes of cells by using their surface markers as inputs and a fluorescein labeled tag for the output. Multiple cell surface markers of “clusters of differentiation” (CDs), i.e., CD45, CD20, CD3, and CD8, were selected as the examples of inputs. In this noble example, blood components did not interfere with the strand displacement cascades; however, the conjugation of DNA with antibodies generally limited the capability of DNA logic circuits to identify more complicated cell targets.

Furthermore, most current DLG biosensors operate only at very high input concentrations, especially for the cases of intracellular logic operations where large amounts of exogenous inputs are generally introduced into cells. While for real-life applications, one of the most critical issues is how to process the logic-gated functions with inputs at their physiological concentrations, which are usually undetectable for logic operations. Meanwhile, the majority of the reported systems are only capable of generating Boolean values with two-inputs at a static concentration, while diagnosis conclusion relays on rapid and simultaneous analysis of complex biomarkers. The power of amplification strategies and DNA computing allows possibility to address this issue. For example, Han’s group recently realized successfully cancer diagnosis by analyzing miRNA profiles of clinical serum samples, using a DNA molecular computation platform, followed an in situ amplification and transformation method for miRNA enrichment. They were able to achieve non-small cell lung cancer diagnosis in 6 hours using a 2 mL serum sample, with an accuracy of 86.4%. The novel approach established by authors combined an in silico data training together with the molecular implementation of a winner-takes-all DNA computation scheme. Although this method requires a complicated design scheme, the idea provides immediate possibilities to perform highly efficient in situ diagnosis based on DNA computation and could inspire more clinical applications of DNA computing.

6 CONCLUSION

Overall, promising results have been achieved with the implementation of DLG-based biosensors for the detection of various targets, by obtaining qualitatively with rapid YES/NO answers. The intrinsic biocompatibility and designability of DNA motivate the building of smart nanodevices operating within living cells. Moving forward, with the development of synthetic techniques, instrumentation, and the power of DNA computing, DLG-based biosensors could become more oriented toward practical bioanalysis. These biosensors capable of Boolean logic operation have the potential as a basis for development of future nanorobotic devices that could perform the advanced biocomputing capabilities and serve as smart theranostic platforms.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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