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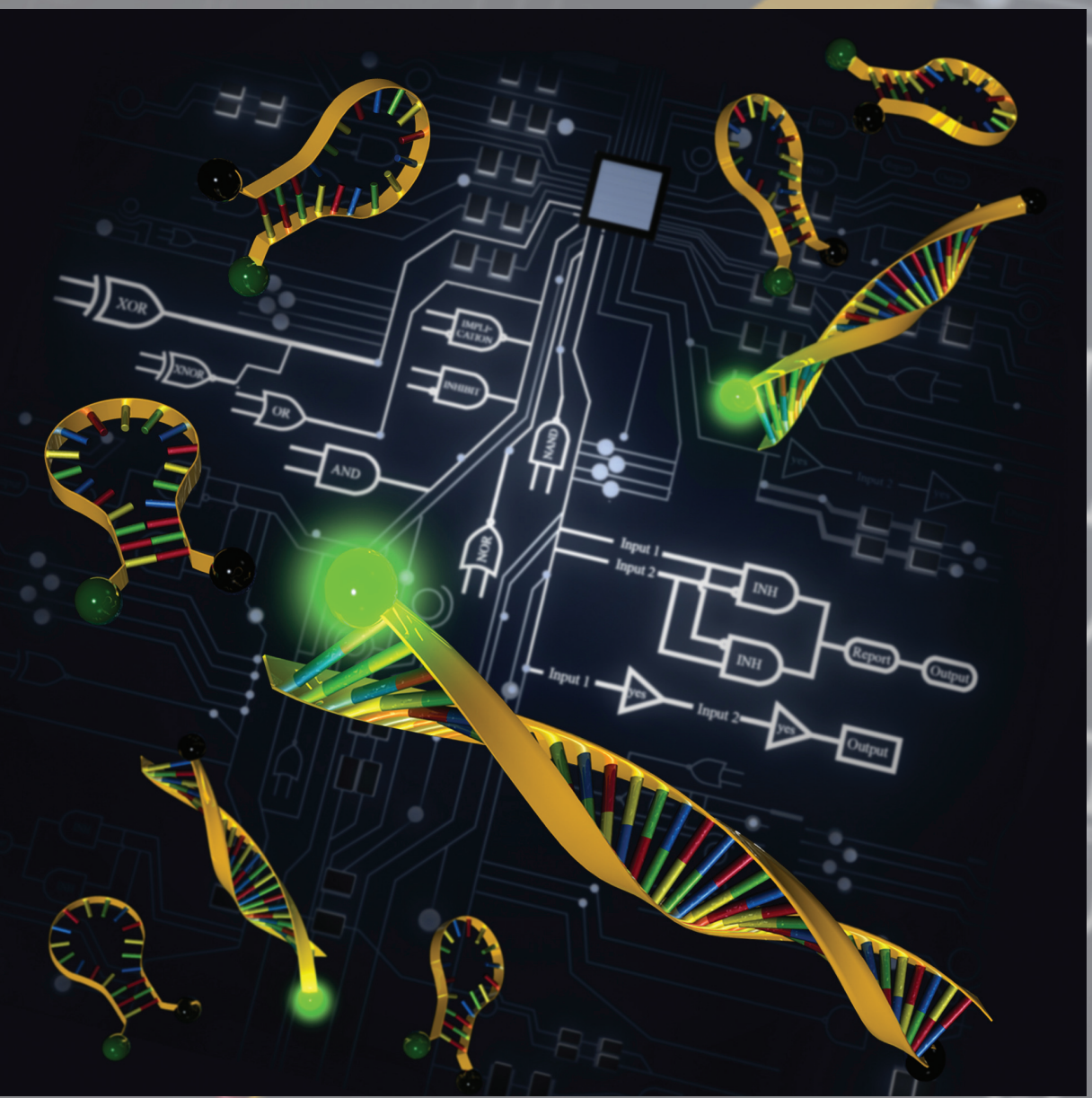

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Simple and Universal Platform for Logic Gate Operations Based on Molecular Beacon Probes
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Logic Gates

Simple and Universal Platform for Logic Gate Operations Based on Molecular Beacon Probes

*Ki Soo Park, Myung Wan Seo, Cheulhee Jung, Joon Young Lee , and Hyun Gyu Park**

***A** new platform technology is herein described with which to construct molecular logic gates by employing the hairpin-structured molecular beacon probe as a basic work unit. In this logic gate operation system, single-stranded DNA is used as the input to induce a conformational change in a molecular beacon probe through a sequence-specific interaction. The fluorescent signal resulting from the opening of the molecular beacon probe is then used as the output readout. Importantly, because the logic gates are based on DNA, thus permitting input/output homogeneity to be preserved, their wiring into multi-level circuits can be achieved by combining separately operated logic gates or by designing the DNA output of one gate as the input to the other. With this novel strategy, a complete set of two-input logic gates is successfully constructed at the molecular level, including OR, AND, XOR, INHIBIT, NOR, NAND, XNOR, and IMPLICATION. The logic gates developed herein can be reversibly operated to perform the set-reset function by applying an additional input or a removal strand. Together, these results introduce a new platform technology for logic gate operation that enables the higher-order circuits required for complex communication between various computational elements.*

1. Introduction

In conventional silicon-based electronics, integrated circuits are assembled from elementary logic gates which are capable of performing all types of Boolean logic by receiving electronic inputs representing true (1, high voltage) or false (0, low voltage) and then generating the appropriate electronic outputs.[1,2] The current technique used to construct silicon-based electronic devices, however, typically relies on lithographic processes in a top-down manner. This method is limited when attempting to achieve the minuscule minimum feature size necessary for highly integrated circuits. Thus, the technology is struggling to keep up with the ongoing miniaturization of the electronic components that are essential in modern information technology to construct more powerful microprocessors.[3–5]

In recent years, it has been suggested that building molecular circuits in a bottom-up manner is a promising alternative means of circumventing the miniaturization limitations associated with the top-down approach.[6–8] Along this line, considerable research efforts have been dedicated to chemical and biological systems that are capable of performing logic operations at the molecular level.[9–17] In particular, nucleic acid has attracted considerable attention as a basic component in the construction of molecular logic gates due to its unique features, including its structural simplicity, straightforward sequence-specific hybridization between complementary strands, and its ability to capture certain target molecules such as metal ions, small molecules, and proteins in a highly specific manner.[18–32] Based on these unique features, a large number of novel logic gate systems have been investigated, but the number of logic gates accomplished by most existing DNA logic gate systems is quite limited, consequently hampering the construction of more complex logic circuits. In addition, unlike electronic systems that share a common Input/Output (I/O) signal (the electron), I/O incompatibilities

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(e.g., metal ions as inputs and fluorescent emissions as outputs) inhibit the assembly of interconnected multi-level circuits with varying degrees of complexity.[17–21,23–25]

Herein, we have developed a simple and universal platform technology to perform a complete set of two-input logic gates (OR, AND, XOR, INHIBIT, NOR, NAND, XNOR, and IMPLICATION) at the molecular level. The system essentially relies on the molecular beacon (MB) probe as a universal component, which is a specifically designed hairpin-structured DNA sequence modified with the fluorophore and quencher at both ends. Single-stranded DNA is used as the input to induce a conformational change of the MB probe, and the resulting fluorescence variation accompanied by the opening of the MB probe is used as the output readout. Based on this strategy, we successfully accomplished the entire set of two-input logic gates at the molecular level for the first time.

2. Results and Discussion

The logic gates constructed herein basically rely on the molecular beacon (MB) probe as their basic work unit with single-stranded DNA as the input. The presence and absence of the single-stranded DNA is assigned as the inputs of 1 and 0, respectively and a different set of input strands is applied for each logic gate. The MB probe is a unique hairpin-structured DNA sequence modified by a fluorophore at one end and a quencher at the other end. The MB probe initially forms a stem-loop structure in the absence of input strands, holding the fluorophore and quencher in close proximity, which significantly suppresses the fluorescence emission of the fluorophore by static quenching. In contrast, the presence of input strands, which are complementary to the MB probe, forces the stem helix to open through their hybridization, at which point fluorescence is restored due to the spatial separation of the fluorophore from the quencher.[33–36] The initial quenched form of the MB probe is given a false operating output value of 0 and the fluorescent state induced by the input strands is assigned a true operating output value of 1.

First, the activation of the MB probe upon hybridization with a specific DNA oligonucleotide was confirmed by checking the thermal profiles of the MB probe and its hybrids with a non-matched random sequence or a perfectly matched sequence (Supporting Information (SI), Figure S1). As illustrated in the SI, Figure S1, the melting temperature (Tm) of the MB probe (curve a) and a hybrid probe hybridized with the perfectly matched sequence (curve c) was 65 °C and 49 °C, respectively. On the other hand, there was no change in the Tm of the MB probe as caused by the presence of a non-matched random sequence (curve b). These results indicated that the designed MB probe correctly formed the hairpin structure and was properly activated only by the perfectly matched DNA sequence. Thus, this MB probe was employed as a universal component for the construction of the molecular logic gates throughout this study.

A complete set of two-input logic gates, OR/NOR, AND/NAND, XOR/XNOR and INHIBIT/IMPLICATION, was then constructed by employing single-stranded DNA as the input. The fluorescent signal enhancement resulting from the conformational change of the MB probe was then used as the output readout. **Figure 1**(a) depicts the design of the OR

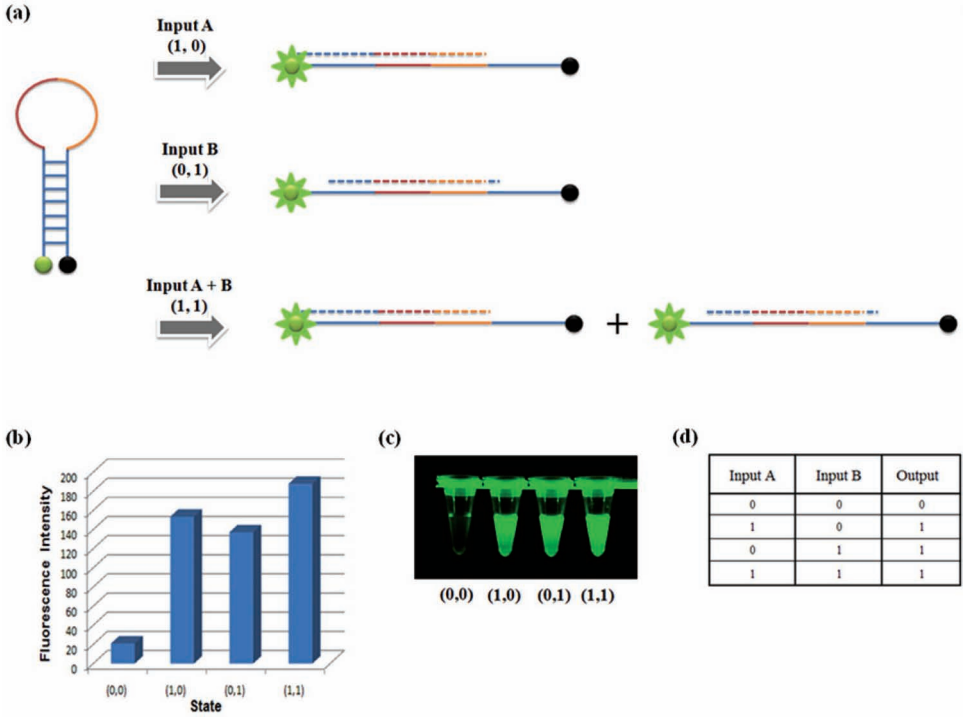

Figure 1. A molecular "OR" logic gate. a) Illustration of the operational design of the "OR" gate. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity measured at 520 nm. c) The corresponding fluorescence image. d) The truth table. State: (0, 0) without (w/o) DNA Input A and B; (1, 0) with (w/) DNA Input A, w/o DNA Input B; (0, 1) w/o DNA Input A, w/DNA Input B; (1, 1) w/ DNA Input A and B.

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logic gate, which produces an output of 1 when at least one of the two inputs is 1. The gate was achieved by applying two inputs, A and B, covering slightly different parts of the MB probe: Input A is complementary to the loop domain and to one complete arm sequence, participating in the stem formation of the MB probe, whereas Input B is also complementary to the loop domain but is partly complementary to both arms of the MB probe. These input strands are designed to be complementary not only to the loop sequence but also to the arm sequence of the MB probe. Therefore, the arm sequence is subjected to hybridization with the input strands when the MB probe is open, while it forms a stem structure with other arm sequence when it is closed. This allows the MB probe to form more stable duplexes with input strands compared to a conventional MB probe, where the stem sequence is not involved in the hybridization process with the input target sequence.[37,38] As a result, either of the DNA inputs, A or B, as well as the two inputs together, can activate the MB probe by binding to each corresponding domain, causing a conformational change with an increase in the fluorescence signal which is in accord with the proper execution of the OR logic gate (Figure 1).

Figure 2 shows the operation of the AND logic gate, which gives an output of 1 only if both of the two inputs are held at 1. The AND gate is constructed by employing the same MB probe used in the OR system as the basic work unit. The universal use of the same MB probe offers a very advantageous feature to our logic gate system, as it allows our system to be universally operated for many different types of molecular logic gates by simply changing the input strands for various logic gates while retaining the MB probe as a universal component. The AND gate is designed such that the addition of either Input A or B, which is partially complementary to the half sequence of the MB probe at each opposite end, cannot activate the MB probe, leaving the MB probe in the closed form. Only when both the inputs, A and B, are applied is the MB probe opened via the cooperative binding of the two inputs. These Inputs, A and B, are selected through the optimization with the candidate input strands which have different degree of complementarity with the half sequence of the MB probe. As expected, the high fluorescent signal, the true output of 1, was successfully generated only from the input state (1, 1), but not from the (1, 0) and (0, 1) input states, which demonstrates the proper execution of the AND logic gate at the molecular level (Figure 2).

An XOR logic gate, which has previously proven to be quite difficult to implement at the molecular level,[11] was then constructed. In this gate, a true output of 1 is obtained when

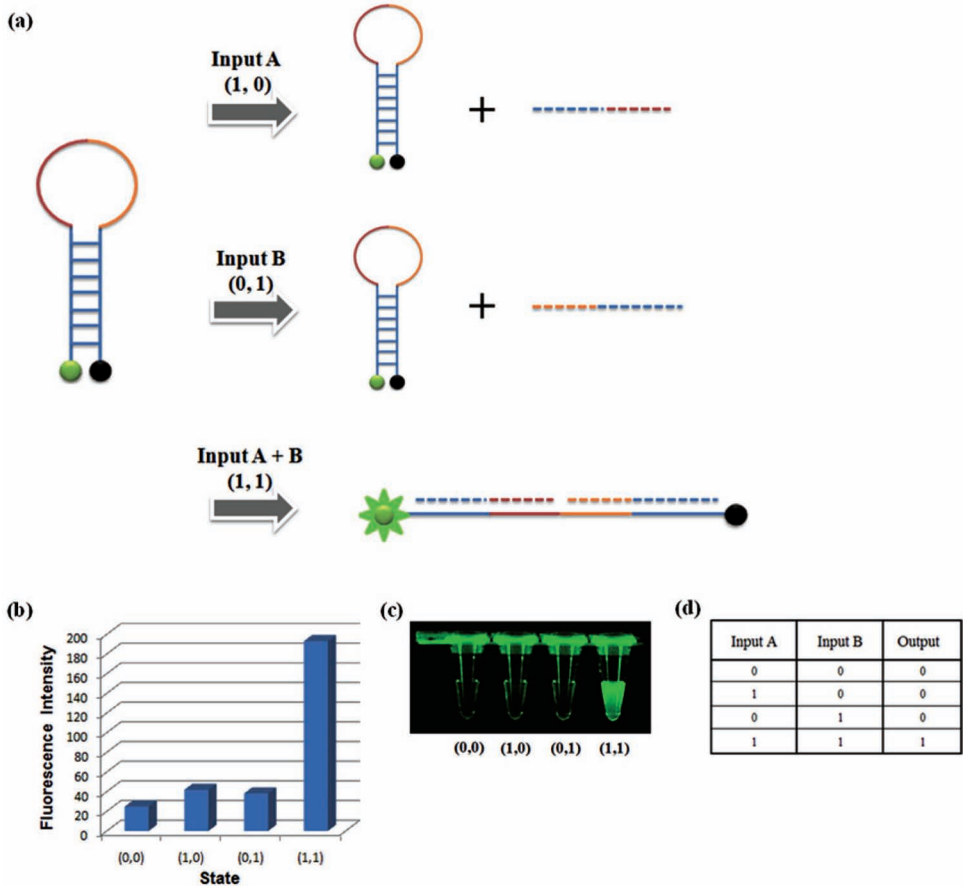

Figure 2. A molecular "AND" logic gate. a) Illustration of the operational design of the "AND" gate. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity measured at 520 nm. c) The corresponding fluorescence image. d) The truth table. State: (0, 0) w/o DNA Input A and B; (1, 0) w/DNA Input A, w/o DNA Input B; (0, 1) w/o DNA Input A, w/DNA Input B; (1, 1) w/DNA Input A and B.

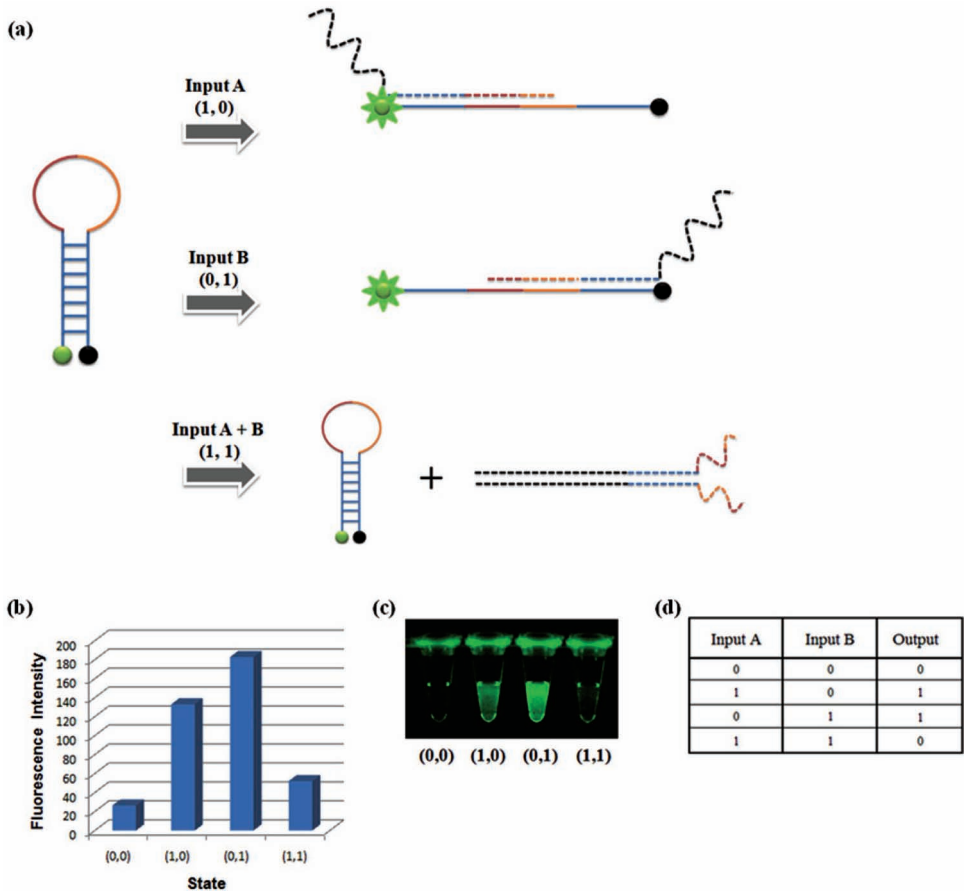

Figure 3. A molecular "XOR" logic gate. a) Illustration of the operational design of the "XOR" gate. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity at 520 nm. c) The corresponding fluorescence image. d) The truth table. State: (0, 0) w/o DNA Input A and B; (1, 0) w/DNA Input A, w/o DNA Input B; (0, 1) w/o DNA Input A, w/DNA Input B; (1, 1) w/DNA Input A and B.

only one of the two inputs is held at 1, whereas a false output of 0 is produced when both inputs are held at either 0 or 1. The two XOR inputs, A and B, are designed to be complementary to the loop and respective entire arm sequence of the MB probe. The MB probe is forced to open through hybridization with either Input A or B, which leads to the fluorescent enhancement caused by the spatial separation of a fluorophore from a quencher within the MB probe. The XOR inputs, A and B, have an additional 15 nucleotides at the respective 3′ and 5′ terminal and these sequences are complementary to each other. Therefore, when both inputs are present simultaneously, the opening of the MB is inhibited because the two inputs A and B preferentially bind to each other instead of binding to the MB probe in a manner necessary to open the MB probe. All of the fluorescent output signals were properly observed in accord with the XOR gate operation (**Figure 3**).

The INHIBIT gate was designed next, the true output of which is generated when only one input is present without the other input (**Figure 4**). This gate is unique in that it behaves non-commutatively, thus being different from the previous commutative OR, AND, and XOR gates.[39] One of the two OR inputs, which is complementary to the entire loop domain and to parts of the two-arm sequences of the MB probe, is again employed as Input A in the INHIBIT logic gate; INHIBIT Input B is designed so that it is perfectly complementary to INHIBIT Input A. Therefore, Input A in this gate opens the MB probe, generating a fluorescent signal much like in the OR logic gate, but the coexistence of Input B prevents the opening of the MB probe by entrapping Input A through hybridization. As demonstrated in Figure 4, the true output of 1 was successfully obtained only when Input A was solely added, which is in accord with proper execution of the INHIBIT logic gate. Together, all of the successful operations of the OR, AND, XOR, and INHIBIT logic gates concretely prove that the employment of a MB probe as a universal component can create a novel platform technology with which to perform logic gate operations at the molecular level.

The above-constructed logic gates always have a false output for the ground state (0, 0) which is 0. However, some logic gates, NOR, NAND, XNOR, and IMPLICATION, require a true value of 1 as the output of the initial ground state (0, 0) for the construction of other types of logic gates.[1] For this purpose, we employed blocker DNA, the middle part of which is complementary to the entire loop domain together with parts of the two-arm sequences of the MB probe. In addition, both ends of the blocker DNA are extended by additional dangling sequences. The MB probe mixed with the

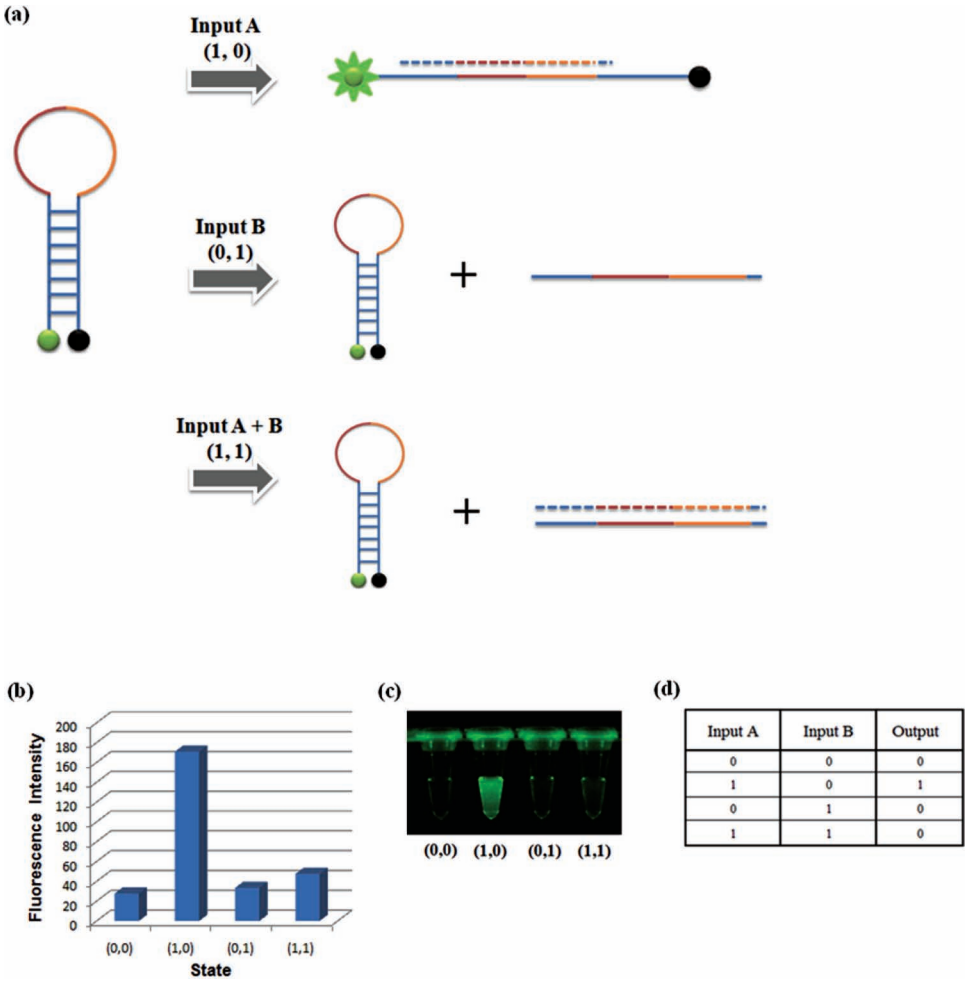

Figure 4. A molecular "INHIBIT" logic gate. a) Illustration of the operational design of the "INHIBIT" gate. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity measured at 520 nm. c) The corresponding fluorescence image. d) The truth table. State: (0, 0) w/o DNA Input A and B; (1, 0) w/DNA Input A, w/o DNA Input B; (0, 1) w/o DNA Input A, w/DNA Input B; (1, 1) w/DNA Input A and B.

blocker DNA was then designated as the ground state (0, 0), which produces an output value of 1 by enhancing the fluorescence signal. Based on this ground state, consisting of the MB probe and the blocker DNA and producing the output of 1, the NOR logic gate was first created, producing the inverted result of the OR gate. Here, the two inputs A and B are designed to be largely complementary to the blocker DNA, as depicted in **Figure 5**(a). Therefore, the presence of either Input A or B as well as both inputs detach the blocker DNA from the MB probe through a strand displacement event, which makes the MB probe return to the closed state and suppresses the fluorescence emission via static quenching. Figure 5(b) and (c) show the results obtained by a fluorescent spectroscopic analysis. The results are consistent with the correct responses of the NOR logic gate.

To probe the universality of the MB-based logic gate system, we also constructed other types of two-input logic gates, the NAND, XNOR, and IMPLICATION. These logic gates generate the inverted result of AND, XOR, and INHIBIT, respectively. Thus, NAND logic should give a true output of 1 for all combinations of binary inputs except for the (1, 1) input state, which should give a false output of 0 (SI, Figure S2). Likewise, XNOR logic should give a true output of 1 if both inputs are held at either 0 or 1, whereas a false output of 0 is produced if only one of the two inputs is applied ((1,0) or (0, 1)) (SI, Figure S3). IMPLICATION logic should give an output of 0 only when one input is present without the other input. More specifically in this logic gate, Input A is complementary to the blocker DNA and dissociates the blocker DNA from the MB probe to force the MB probe to return to its original closed form. On the other hand, Input B is not complementary to the blocker DNA but is exactly complementary to Input A. Therefore, Input B prevents Input A from dissociating the blocker DNA from the MB probe through its hybridization with Input A and leaves the MB probe in an open form (SI, Figure S4). As a result of all of these rational designs of the two input strands, the fluorescent output signals resulting from the input states (0, 0), (1, 0), (0, 1), and (1, 1) successfully mimic those of an electronic NAND, XNOR, and IMPLICATION gate. It is noteworthy that two separate DNA strands, which were Input A and B for AND logic gates, were again employed as

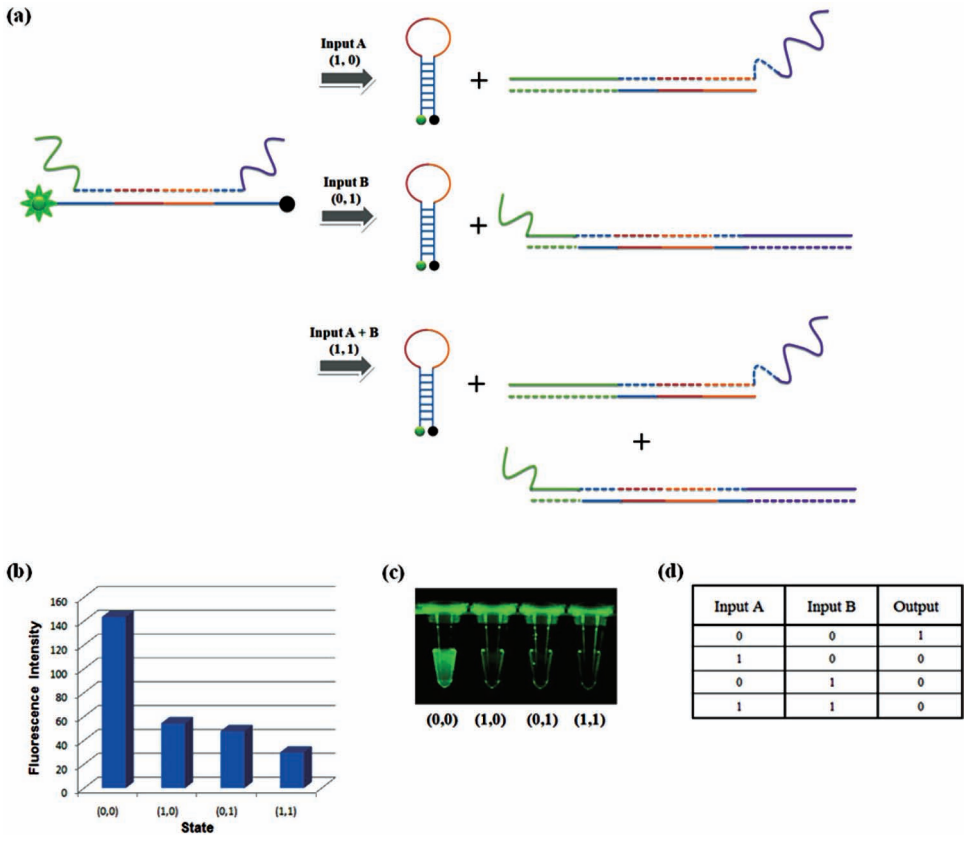

Figure 5. A molecular "NOR" logic gate. a) Illustration of the operational design of the "NOR" gate. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity measured at 520 nm. c) The corresponding fluorescence image. d) The truth table. State: (0, 0) w/o DNA Input A and B; (1, 0) w/DNA Input A, w/o DNA Input B; (0, 1) w/o DNA Input A, w/DNA Input B; (1, 1) w/DNA Input A and B.

the blocker DNA in the XNOR and IMPLICATION logic gates while a single DNA strand was sufficient as the blocker DNA to construct the NOR and NAND logic gates.

To demonstrate the gate networking necessary for the higher-order circuits with varying degrees of complexity, a multi-level circuit (MC) was constructed. As a proof-of-concept, two INHIBIT logic gates separately operated with different MB probes were combined to form a multi-level circuit that enforced an overall XOR Boolean behavior (**Figure 6**). Here, a newly designed MB probe, denoted as MB (B), was employed in addition to the originally used MB probe, which is denoted as MB (A). The operation of the additional MB (B)-based INHIBIT (2) logic gate was confirmed using the corresponding inputs (SI, Figure S5) together with the previously verified MB (A)-based INHIBIT (1) (Figure 4). MC Input A, compatible with both of the INHIBIT gates, (1) and (2), was newly created by combining the two sequences of INHIBIT (1) Input A, which forces MB (A) to open, and INHIBIT (2) Input B, the complement of INHIBIT (2) Input A. Similarly, by connecting INHIBIT (2) Input A, which forces MB (B) to open, with INHIBIT (1) Input B, the complement of INHIBIT (1) Input A, MC Input B was generated. Both MB (A) and (B) in the same solution were exposed to the two inputs of MC Input A and B. Consequently, the addition of either MC Input A or B activates its respective MB probe, which leads to the enhancement of the fluorescent signal. On the other hand, the two inputs were preferentially hybridized with each other due to their complementarity, thus preventing the opening of MB (A) and (B) when both of the inputs were added simultaneously (Figure 6). This result demonstrates that the multi-level circuit, which was constructed from the differently operated INHIBIT logic gates (1) and (2), successfully executes the overall XOR Boolean behavior.

We also proved that the output of one gate in our system could be used as the input for the downstream gate based on the sequence-addressability of DNA, which verifies the possibility of communication within a network of gates. Here, stem-loop structured DNA without the fluorophore and quencher at both ends was employed as MB (1), and Input (1) was designed to be complementary to the loop sequence of MB (1) for the construction of the first YES gate. The presence of Input (1) opens MB (1) through the hybridization of the loop domain. Importantly, the single-stranded one-arm sequence in the open form of MB (1), the output of the first YES gate, serves as Input (2), subsequently interacting with MB (2), which contains the fluorophore and quencher pair at the ends. This consequently results in the opening of MB (2) with a concomitant fluorescent increase (**Figure 7**).

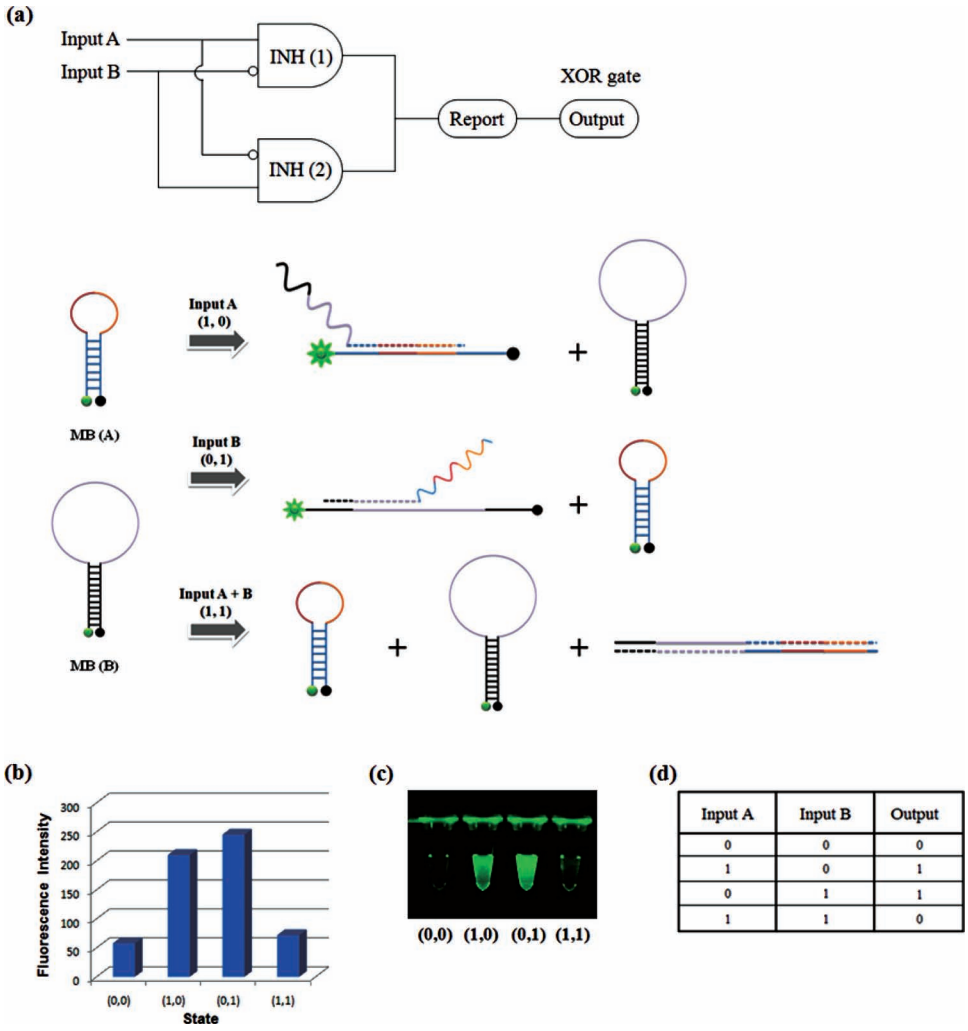

Figure 6. Multi-level circuit built from two independently operated "INHIBIT" gates for the overall "XOR" analysis of the inputs. a) Illustration of the operational design of the multilevel circuit. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity measured at 520 nm. c) The corresponding fluorescence image. d) The truth table. State: (0, 0) w/o DNA Input A and B; (1, 0) w/DNA Input A, w/o DNA Input B; (0, 1) w/o DNA Input A, w/DNA Input B; (1, 1) w/DNA Input A and B.

In electronic memory devices, the set-reset function is important to store information in a write-read-erasable form.[40,41] Thus, it is necessary for the initial state of the system to be recovered by means of proper manipulation.[42–44] In order to meet this demand, a removal strand (Rs) is employed to detach the input strand (Is) from the MB probe via a strand displacement event mediated by sequence-specific DNA recognition. Specifically, Rs is designed to bind to the dangling region of Is which was previously bound to the MB probe and then displace the Is. Consequently, the waste duplex (Wd), composed of hybridized Is-Rs, diffuses away, allowing the MB probe to return to its initial closed state. The effective operation of the recycling procedure was monitored by the fluorescence signal of the MB probe, and it was confirmed that the reversible OFF (0, low fluorescence)–ON (1, high fluorescence) switching was well operated by the successive addition of Is and Rs (**Figure 8**).

To verify the set-reset function of our logic gate system, we employed a XOR logic gate which was correctly operated with the corresponding input strands, as previously confirmed in Figure 3 and in the SI, Figure S6 (a). By applying removal strands to the XOR logic gate, the initial state of the system was successfully recovered (SI, Figure S6 (b)). Importantly, the appropriate output signal in accord with XOR logic was again produced when the XOR inputs were also added to the recovered system (SI, Figure S6 (c)). This clearly confirms that the MB-based logic gates could perform the set-reset function, which permits the development of memory devices that are capable of storing information in a write-read-erasable form.

3. Conclusion

We have successfully constructed a complete set of two-input logic gates (OR, AND, XOR, INHIBIT, NOR, NAND, XNOR, and IMPLICATION) at the molecular level by employing a MB probe as the basic work unit and very rationally designing

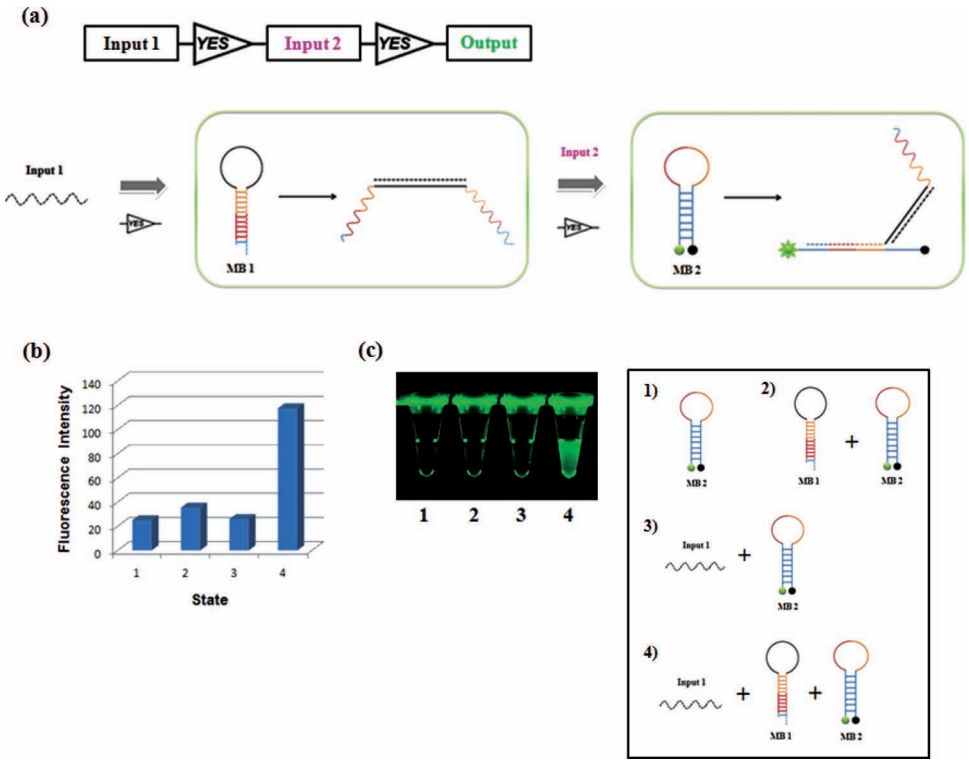

Figure 7. The gate wiring to permit more complex logic circuits. a) Illustration of the operational design of the gate wiring. The output of the first "YES" gate can serve as the input to the second "YES" gate. Solid and dashed line segments of the same color are complementary to each other. b) The fluorescence intensity measured at 520 nm. c) The corresponding fluorescence image. State: 1. w/only MB (2); 2. w/MB (1) and MB (2); 3. w/MB (2) and Input (1), which activates the first "YES" gate; 4. w/MB (1) and MB (2) together with Input (1), which activates the first "YES" gate.

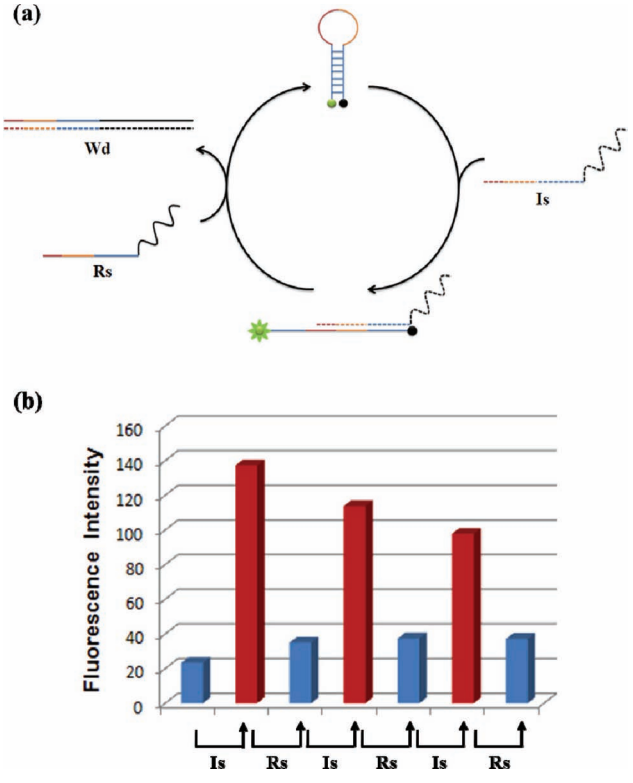

Figure 8. a) ON-OFF switch cycles upon the successive additions of input strand (Is) and removal strand (Rs). b) The resulting fluorescence output signal measured at 520 nm. Waste duplex (Wd).

a series of inputs to perform the corresponding logic gate operations. This simple but universal system is based in principle on the strand displacement process conferred by the sequence-specific recognition properties of DNA, which allows it to disrupt interactions within the MB probe. In addition, gate wiring into multi-level circuits, which is necessary for the creation of molecular circuits with increased complexity and computational utility, was demonstrated by combining separately operated logic gates or assigning the DNA output of one gate as the input to the next gate. Importantly, this simple but versatile logic gate system can be reversibly operated by the successive addition of input and removal strands, which permits the set-reset function to be achieved. This work to construct a complete set of two-input logic gates is expected to provide researchers with a rigid experimental basis for the construction of more complex logic systems. It can also serve as a novel platform technology upon which to build molecular circuits in a bottom-up manner.

4. Experimental Section

Materials: All of the DNA oligonucleotides used in the present study were synthesized and purified using HPLC and were confirmed using a MALDI–TOF system by Integrated DNA Technologies, Inc. (Coralville, IA). The sequences of the DNA oligonucleotides are listed in the SI, Table S1. The stock solutions of DNA oligonucleotides were prepared in ultrapure DNase/RNase-free distilled water

purchased from Invitrogen and quantified using UV-vis absorption spectroscopy with the following extinction coefficients (ε_{260}, M^{-1} cm^{-1}) for each nucleotide: A = 15 400, G = 11 500, C = 7400, and T = 8700. After dilution to the required concentrations with ultrapure water, the DNA solutions were used for the construction of the molecular logic gates. All other chemicals of analytical grade were purchased from Sigma-Aldrich and were used without further purification.

Instrumentation: To measure the DNA concentration, absorption intensities were recorded at λ = 260 nm using a Cary 100 UV-vis spectrophotometer (Varian, Palo Alto, CA). Fluorescence spectra were captured using a RF-5301 PC spectrophotometer (Shimadzu, Japan) with excitation at 485 nm (5 nm bandwidth) and emission at 520 nm (5 nm bandwidth). The corresponding image was scanned by a cooled charge-coupled device camera (Fuji Film, Japan) with a constant focal plane, magnification, and integration time. To determine the thermal profiles of the MB probe and its target, the fluorescence intensity at 520 nm for fluorescein was measured on a C1000 thermal cycler (Bio-Rad, CA, USA) as the temperature was increased from 20 °C to 90 °C in steps of 2 °C, with each step lasting 2 min.

General Method: A complete set of two input logic gates was prepared in a hybridization buffer (10 mM Tris-HCl pH 7.9, 50 mM NaCl, and 10 mM $MgCl_2$). To perform the logic gate operations of OR, AND, XOR, and INHIBIT, which generate an output of 0 at the ground state (0, 0), the basic work unit, the MB probe at a concentration of 1×10^{-7} M, was first mixed with the respective DNA inputs at a concentration of 1×10^{-7} M in a hybridization buffer. The solutions were then heated to 90 °C for 5 min to dissociate any intermolecular interaction, after which they were slowly cooled to room temperature and incubated for 30 min. From each of the samples, an amount of 50 µL was transferred to a cuvette and the resulting fluorescent output signal was recorded at 520 nm for fluorescein.

For the construction of other types of logic gates, NOR and NAND to generate a true value of 1 at the ground state (0, 0), the same procedure used with the above-mentioned assay was employed again, except that blocker DNA at a concentration of 1×10^{-7} M was also added. For the construction of XNOR and IMPLICATION to generate a true value of 1 at the ground state (0, 0), the same procedure used for the above-mentioned assay was employed again, except in this case two blocker DNAs at a concentration of 1×10^{-7} M were also added.

For the gate wiring into multi-level circuits (MC), MB (B) with a different DNA sequence in addition to MB (A) at a concentration of 1×10^{-7} M was employed. Both MB (A) and (B) in the same solution were exposed to MC inputs A and B at a concentration of 1×10^{-7} M and operated in the same manner described for the above-mentioned assay.

To prove that the output of one gate can be used as the input for the next downstream gate, MB (1) without a fluorophore and quencher at both ends and Input (1), complementary to the loop sequence of MB (1), were employed at a concentration of 1×10^{-6} M and 2×10^{-6} M, respectively, for the construction of the first YES gate. MB (2), containing a fluorophore and quencher pair at the ends, was used at a concentration of 1×10^{-7} M for the construction of the next YES gate. The resulting output fluorescent signal was recorded at 520 nm.

The set-reset function was validated by exemplifying XOR logic gates and designing the removal strands, which were the complement of the input strands. Reversible operation was achieved by the successive addition of input strands and removal strands at a concentration of 1×10^{-7} M in a hybridization buffer containing a MB probe at a concentration of 1×10^{-7} M.

A universal threshold of F_{520} = 60 was chosen to define a false output of 0 ($F_{520} < 60$) and a true output of 1 ($F_{520} > 60$) of all the logic gates.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

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