Communication

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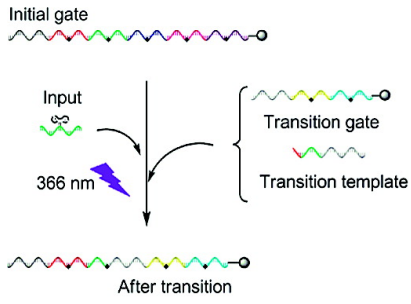

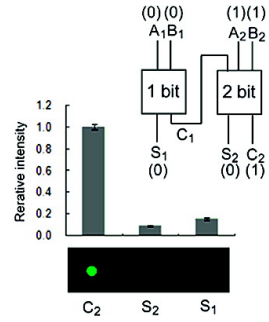

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Autonomous DNA Computing Machine Based on Photochemical Gate Transition

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A major challenge in molecular computing is to construct logic gates that are devices that perform the fundamental logic operations NOT, AND, and OR, as well as their combination including full-adder. In particular, DNA has proven to be highly useful as building blocks for the construction of logic gates in several molecular logic gates[1–5] because DNA offers immense information-encoding capacity and predictable recognition through well-defined Watson−Crick complementarity.[6–8] In the past few years, many types of DNA-based logic gates were reported such as deoxyribozyme,[9,10] DNA tile,[11,12] and telomere DNA structure.[13] We recently developed the photochemical DNA logic gates "NOT, AND, OR, and full-adder", which implement the sequence-specific photocleavage (SSPC) of photo-cross-linking sites via carbazole-modified oligonucleotide (ODN).[14] Although basic logic gates can be easily assembled by the above systems, complicated logic circuits, for example, binary digit addition that is a key operation in information processing, can not, due to the difficulty of constructing an autonomous cascading system using DNA. As an example of autonomous DNA computing, Beneson and co-workers have developed a programmable finite automaton comprising DNA and DNA-manipulating enzymes that solves computational problems autonomously.[15] In their method, computing was autonomously carried out by repetitive cycles of restriction, hybridization, and ligation reactions in a single mixture. They made compromises in choosing the condition to partially satisfy both enzymes because restriction enzyme and ligase require different conditions for optimal efficiency.

Here, we report the construction of autonomous DNA computing based on photochemical gate transition and the operation of binary digit addition using this system. In our method, both photochemical DNA manipulations previously reported, photoligation via 5-carboxyvinyldeoxyuridene (^{cv}U) containing ODN[16] and photocleavage via carbazole-modified ODN,[14] were employed. The photochemical approach offers the potential advantages of extremely high efficiency >95%, sequence specificity, less restricted reaction conditions, high handle ability, and easy automation.

As shown in Figure 1a, binary digit addition can be realized by a combination of full-adder whose function is to take three binary inputs and add them together to produce two binary outputs known as the sum (S) and the carry (C). To obtain S_n and C_n for n bit, output C_{n-1} (0 or 1) for $n-1$ bit is cascaded as the input of n bit. From the Boolean expression of the binary digit addition (Figure 1b), we found that gate switching, "AND" or "OR" for C_n, and "XOR" or "XNOR" for S_n, was carried out according to previous output C_{n-1} (0 or 1). We constructed this switching system by using photochemically induced autonomous gate transition (photocleavage, hybridization, and photoligation). The system has four components: initial gate, carbazole-modified input, transition gate, and transition template. The initial gate consisted of the AND gate for C_1 and the XNOR (or OR) gate for S_2 (or C_2). The transition gate contained the 23-mer complementary sequence with a transition

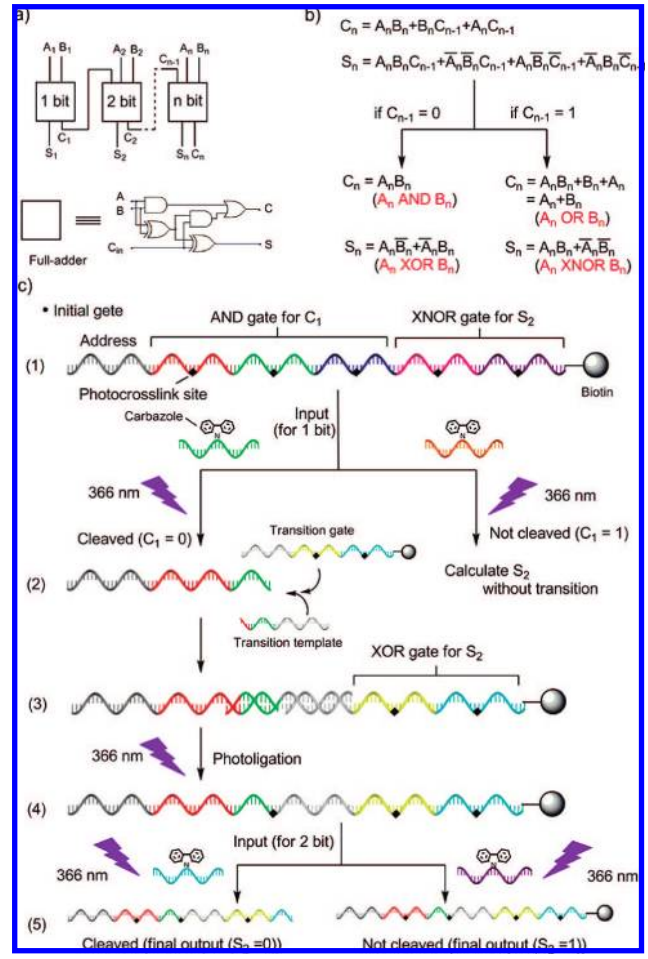

Figure 1. (a) Circuit diagram of the binary digit addition. (b) Boolean expression of the binary digit addition. (c) Schematic of gate transition to obtain S_2. The diagrams depict (1) the initial gate possessing the AND gate for C_1, the XNOR gate for S_2, and the address for the readout using the DNA chip, (2) the initial gate cleaved by 366 nm irradiation via carbazole-modified input (only match input with the C_1 region), (3) the transition state combined with the transition gate possessing the XOR gate for S_2 through the transition template, (4) the complete transition state by 366 nm irradiation, and (5) the final output. The above events autonomously occur in a single test tube by 366 nm irradiation.

template at the 3′-end and the XOR (or AND) gate for S_2 (or C_2). Each gate moiety in the initial gate and the transition gate are composed of a linear combination of 23-mer sequences possessing one photo-cross-link site. For the design of 23-mer sequences, the following constraints were applied: similar GC content, uniform thermodynamic behavior, and no self-complementarity. For a readout by the DNA chip, initial gates were addressed in the 5′-

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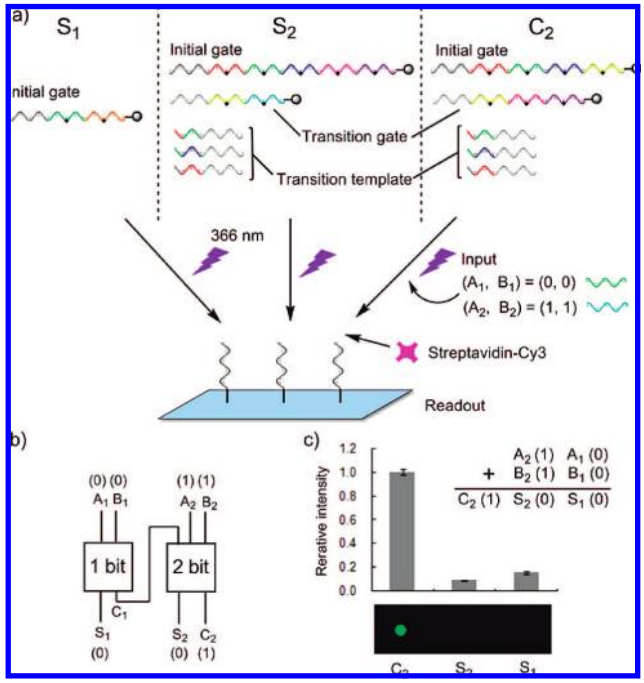

Figure 2. (a) Conceptual scheme of the operating procedure. The initial gate, transition gate, transition template, and appropriate input were mixed in different single tubes S_1, S_2, and C_2, respectively, and then photoirradiated using a transilluminator at 366 nm. For the readout, the streptavidin−Cy3 conjugate was added and applied onto a DNA chip. (b) Circuit schematic of the 2 bit addition. (c) Fluorescence image and relative intensity of binary addition 10 + 10, extremely good agreement with answer 100.

end 23-mer and 3′-labeled with biotin to allow monitoring of fluorescence output with streptavidin−Cy3 interaction.

Figure 1c illustrates the expected photochemical events along the computing process of obtaining S_2. We anticipated that the AND gate for C_1 in the initial gate would be cleaved by photoirradiation to output $C_1 = 0$, only if the input for 1 bit was match sequenced to the AND gate. Next, the computation proceeded via photoligation of the transition gate involving the XOR gate for S_2 to the cleaved initial gate on the appropriate transition template. The ligation product was then cleaved again by photoirradiation at the XOR gate to output $S_2 = 0$, only if the input for 2 bits was match sequenced to the XOR gate. When the input for 2 bits was not match sequenced to the XOR gate, final output $S_2 = 1$. In contrast, S_2 was calculated by using the XNOR gate equipped with the initial gate when the AND gate for C_1 was not cleaved (i.e., $C_1 = 1$). The above process was autonomously carried out by one-time irradiation in a single test tube.

To examine gate transition using our photochemical method, a mixture of the initial gate, transition gate, and transition template was irradiated at 366 nm in the presence of matched or mismatched input, and absence of input was used as a control. Expectedly, the result showed a clear disappearance of the initial gate and appearance of a new band corresponding to the transition gate, only in the presence of match input with 90% conversion for 2 h, as evidenced by migration of PAGE analysis (see Supporting Information). Following proof of the gate transition system, we performed 16 possible binary additions of two bits as seen Figure 2b ($A_2A_1 + B_2B_1 = 00 + 00$, $00 + 01$, $00 + 10$, $00 + 11$, $01 + 00$, $01 + 01$, $01 + 10$, $01 + 11$, $10 + 00$, $10 + 01$, $10 + 10$, $10 + 11$, $11 + 00$, $11 + 01$, $11 + 10$, $11 + 11$) according to the following steps. First, the initial gate, transition gate, transition templates, and both appropriate inputs, one for 1 bit, and the other for 2 bits, were mixed in different single tubes S_1, S_2, and C_2, respectively. Second, the mixture was incubated at 95 °C for 2 min, then cooled down to room temperature at a rate of 1 °C per min, and then photoirradiated with a transilluminator (366 nm) at room temperature for 5 h. Finally, the streptavidin−Cy3 conjugate was added to the reaction mixture, before applying it to a DNA chip for readout (Figure 2a). The fluorescence results corresponded to the correct answers to the all of the 16 possible binary additions. For example, the assignment ($C_2 = 1$, $S_2 = 0$, $S_1 = 0$) satisfies the answer to binary addition 10 + 10 (Figure 2c).

In summary, we successfully constructed a one-pot autonomous DNA computing machine using the photochemically induced gate transition (photocleavage via carbazole-modified ODN, hybridization, and photoligation via ^{cv}U) and performed the 16 possible binary additions of 2 bits using this machine. The fluorescence readout by the DNA chip showed good agreement with correct answers to all of the 16 possible binary additions. Although there is a sequence limitation associated with use of the artificial nucleobases, our photochemical method provides several distinctive advantages including high efficiency, less restricted reaction conditions, high handle ability, and easy automation compared to the enzymatic method. This photochemical DNA machine is easily applicable to correlation analysis between SNPs as well as other binary digit processing, such as subtraction.

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Supporting Information Available: Experimental conditions and sequence of gate strands used in binary digit additions. Detail of photochemical gate transition mechanism for the S_2 and C_2. Results from all binary additions, and control experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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