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RESEARCH PAPER

Optofluidic DNA computation based on optically manipulated microdroplets

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Abstract DNA computing is a promising approach for dealing with biomolecular information. Although several DNA logic circuits which can evaluate biomolecular inputs have been proposed, they have serious drawbacks in the processing speed and the amount of molecules used in implementation. Here, we present optofluidic DNA computation as an effective method for constructing a DNA computing system. By confining the reaction space of DNA computation to the inside of a microdroplet and manipulating a group of droplets with external light signals, we improve usability of DNA computation as well as the processing performance. Optical manipulation is applied to transport the droplets and to initiate DNA computation by forced merging of the droplets. The proposed method has advantages over conventional DNA computation schemes in flexible operations, simultaneous multiplexed evaluation, and processing acceleration. As the first demonstration of optofluidic DNA computation, logical AND and OR operations are performed by optical manipulation of microdroplets which contain either DNA logic gates or input molecules. Also, considerable reduction in the processing time is confirmed on the optofluidic DNA computation owing to reduction of the reaction space to the microdroplet.

Keywords Optofluidics · DNA computing · Microdroplets · Optical manipulation · DNA logic operation

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1 Introduction

DNA computation is an efficient and promising approach for realizing molecular-based information processing that utilizes the features of DNA, such as the capabilities of recognizing biomolecules and autonomous reactions based on Watson–Crick complementarity (Benenson 2009). Several studies have been published concerning DNA logic gates and circuits in which binary signals represented by biomolecular presence are processed using biochemical reactions (Mao et al. 2000; Stojanovic et al. 2003; Benenson et al. 2004; Seeling et al. 2006; Yoshida et al. 2007; Qian et al. 2011). DNA logic circuits composed of multiple DNA logic gates exhibit computational scalability, which can be used to extend the scale of the target problem (Qian et al. 2011). Since DNA computation handles both molecular information and the material simultaneously, it might be useful in analysis and control of complicated molecular environments such as biological systems.

Despite these attractive features, DNA logic circuits have serious drawbacks in the processing speed and the amount of molecules used in implementation (Reif 2011). To increase the processing throughput of chemical reactions, droplet-based microfluidic systems have been proposed (Huebner et al. 2008; Teh et al. 2008; Dittrich et al. 2006). These systems possess remarkable features such as a compartment for the reactants, reduction of reactant molecules and high processing throughput. Several attempts of DNA computation based on the microfluidic system have been demonstrated (Grover et al. 2005; Zhang et al. 2009). The use of microdroplets enables the control of molecular positions and confinement of the reaction within the unit of a droplet.

Although a simple processing task can be implemented by conventional microfluidic schemes, minute and

complicated operations are difficult to perform. As a solution, the authors introduced optical manipulation to extend the capability of the droplet-based microfluidic system. The optical manipulation technique has following advantages: easy implementation, accurate operation and non-invasiveness. In addition, this technique does not require fabrication of reaction vessels and reconfigurability (Gahagan et al. 1998; Sasaki et al. 1992; Reiner et al. 2006; Lorenz et al. 2007; Ogura et al. 2011a). This method improves the performance of DNA computation with respect to processing speed and controllability of the processing.

In this paper, we present optofluidic DNA computation as an effective method for constructing a DNA computing system based on optically manipulated microdroplets. Optofluidic DNA computation is an integrated scheme of DNA computation, droplet-based microfluidics and optical manipulation. It aims to improve the processing performance of DNA computation as well as usability of the emerging technology. As the first demonstration of the optofluidic DNA computation, logical AND and OR operations are implemented and significant reduction in the processing time is confirmed.

2 Optofluidic DNA computation

The fundamental scheme of optofluidic DNA computation is illustrated in Fig. 1. Most DNA computation techniques utilize DNA reactions by which single strands of DNA hybridize with their complementary DNAs, strand displacement and conformational change. Microdroplets composed of water distributed in an oil solution are employed. An individual water-in-oil microdroplet encapsulates the molecules comprising of DNA logic gates or input signals and preserves them until the time of gate operation. To initiate the gate operation, the necessary microdroplets are gathered and forced to be merged by optical manipulation. The entire operation can be performed remotely with external light signals.

Microdroplets also function as transport containers. They can be transported flexibly by adequate control of optical radiation pressure force (Gahagan et al. 1998; Sasaki et al. 1992) and fused (Lorenz et al. 2007; Ogura et al. 2011a) easily without using microfabricated structures. Independent and parallel manipulation of microdroplets is achievable by generating appropriate optical field patterns dynamically with a spatial light modulator (SLM) (Ogura et al. 2011a; Prentice et al. 2004; Eriksen et al. 2002), and different compositions of DNA logic gates are configured at multiple positions simultaneously. The individual molecular elements are separated into different microdroplets and transported for the desired operation by optical manipulation. This form of operation increases controllability and flexibility of DNA computation. For example, it is possible to configure next operation dynamically or to select microdroplets according to the previous result in the microdroplets.

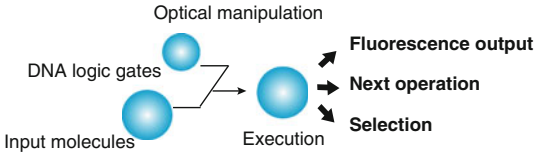

Fig. 1 *Conceptual diagram* of an optofluidic DNA computation

The use of microdroplets accelerates the processing speed of DNA computation. In a typical DNA computation, signals between the logic gates are often cascaded using diffusion of signal DNAs (Seeling et al. 2006; Qian et al. 2011) such that the processing speed is restricted by the diffusion time. For reducing the diffusion time, reduction of the reaction space is effective. In particular, employment of pico- or femtoliter volume of microdroplets is a reasonable method for this purpose.

3 Method and materials

3.1 Optical manipulation of microdroplets

An object with lower refractive index than that of the surrounding medium, such as a water-in-oil microdroplet, receives repulsive force from a focused beam, such that single-beam trapping of the low-index object is not achievable. To overcome this limitation, methods using beam scanning (Sasaki et al. 1992), optical vortex (Gahagan et al. 1998; Lorenz et al. 2007) or a spot-array pattern (Ogura et al. 2011a) have been developed to manipulate and fuse water-in-oil microdroplets. In this study, we adopt the spot-array pattern method for this purpose. This method allows simple generation of light intensity distributions for transportation and fusion of microdroplets and ease in increasing the number of manipulated microdroplets simultaneously. Figure 2a shows a schematic manipulation and fusion of the microdroplets with spot-array patterns. DNA nanocomputing devices or input molecules are encapsulated in aqueous microdroplets in an oil solvent without leakage. A single microdroplet can be manipulated by composition of repulsive forces from multiple laser spots, and two or more microdroplets are transported and fused after the contact. As previously demonstrated, simultaneous reactions at different positions by optical manipulation of microdroplets with spot-array patterns can be achieved (Ogura et al. 2011a), and this method is suitable for operating DNA logic gates.

3.2 Optical setup

The optical setup is shown in Fig. 2b. The system is based on a microscope (BX-51, Olympus, Japan) that enables bright-field and fluorescence observation. A helium–neon laser (wavelength: 632.8 nm, output: 25 mW) was used for the light source of optical manipulation. An SLM (X10468-01, Hamamatsu Photonics, Japan) was employed to generate hologram patterns dynamically. A collimated laser beam was modulated by the SLM, and a hologram pattern was generated at the sample plane through a Fourier-transforming lens L2 and reduction optics consisting of lenses L3 and OL1. Computer-generated holograms (CGH) were designed using an iterative algorithm based on the optimal rotation angle method (Bengtsson et al. 1994). The CGHs prepared previously for microdroplet manipulation were changed sequentially. A halogen lamp served as a bright field illumination source. A mirror unit (U-MNIBA3, Olympus, Japan) and a mercury lamp were used for fluorescence observation and light source excitation, respectively. Bright field and fluorescence images were captured by a cooled CCD (CoolSNAP ES, Roper Scientific, USA).

3.3 DNA logic gates

DNA logic gates are fundamental components for computation at a molecular level. We implemented strand-displacement-based logic gates, which were modified from Photonic Boolean logic gates reported by Yoshida et al. (2007) (Fig. 3). The logic gates, which consist of three DNA strands, achieved a two-input AND or OR operation. The input is represented by two short DNA strands with different sequences, I1 and I2. The logical value is 0 when no I1 (I2) exists and 1 when I1 (I2) exists. The logical value of the output of the gate is encoded into a fluorescence signal: the output is 0 for low intensity and 1 for high intensity.

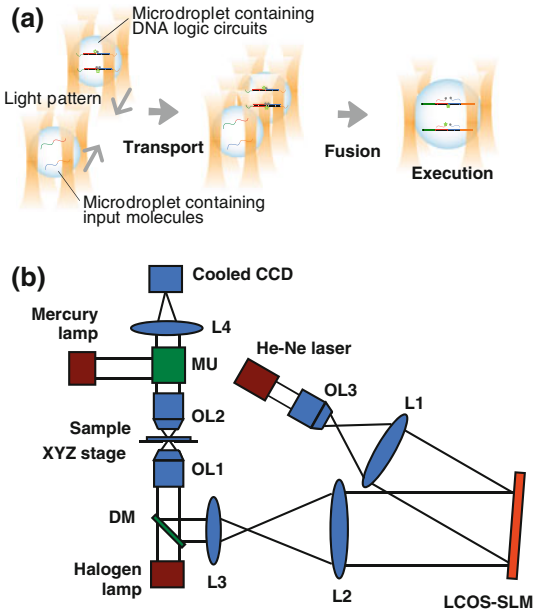

Fig. 2 **a** Schematic of reaction control by optical manipulation. **b** Optical setup. *L1*: $f = 100$ mm, *L2*: $f = 500$ mm, *L3*: $f = 200$ mm, *L4*: $f = 180$ mm, *OL1*: 60 × water immersible objective lens, *OL2*: 100 × water immersible objective lens, *OL3*: 10 × objective lens, *DM* dichroic mirror, *MU* mirror unit

3.4 Microdroplet preparation

Acetophenone (98.5%) (Wako Pure Chemical, Japan) and sorbitan monooleate (Span 80) (Nacalai Tesque, Japan) were used as an oil solvent and a surfactant, respectively, to fabricate microdroplets. Forty microliters of acetophenone and 10 μL of the surfactant were mixed in a test tube and then 10 μL of a DNA solution (concentration: 100 μM) was added to the mixture. The solution was left for 10 min after pipetting. The acetophenone phase containing microdroplets of the DNA solution was extracted. To control and

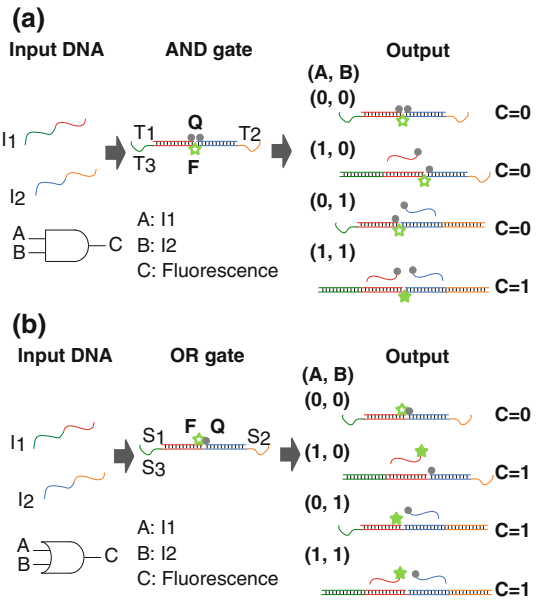

Fig. 3 AND and OR gates used in this study. The gates were modified from photonic Boolean logic gates (Yoshida et al. 2007). **a** The AND gate consists of three types of DNA strands, T1, T2 and T3. T1 and T2 are modified with a black hole quencher (BHQ1), and T3 is modified with calboxyfluorescein (FAM). FAM and BHQ1 is a pair of fluorescence resonance energy transfer (FRET). When I1 (I2) exists, T1 (T2) is replaced because of difference in the binding force to T3. When both I1 and I2 bind to T3, the fluorescence increases because FAM and BHQ1 are apart. In the other cases, the excited energy of FAM transfers to BHQ1 on T1 and/or T2, and the fluorescence intensity remains low. **b** The OR gate works in a manner similar to that of the AND gate. The only difference is the positions of FAM and BHQ1. S1 is modified with FAM and S2 is modified with BHQ1. The fluorescence intensity increases when I1 or I2 binds to S3

Table 1 Sequences and modifications of DNA used in this study

Name	Sequence (5′−3′)
T1	BHQ1-GTCGACCTTCCT
T2	CCAACCACAGTG-BHQ1
T3	AGTATTGCGGAGGAAGGTCGACT*CACTGTGG TTGGTGTGGTTGG (T*is modified with FAM)
S1	FAM-GTCGACCTTCCT
S2	CCAACCACAGTG-BHQ1
S3	AGTATTGCGGAGGAAGGTCGACTCACTGTGG TTGGTGTGGTTGG
I1	TCGACCTTCCTCCGCAATACT
I2	CCAACCACACCAACCACAGT
M	TAMRA-TGACGCTATGGCAAATCGACGGACTG AGCAGCTGGTCTAAGT

observe microdroplets through the microscope, 5 μL of the acetophenone was sandwiched between cover slips (Matsunami Glass, Japan) and sealed. Microdroplets of 5–10 μm in diameter were selectively used in the experiments. DNA modified with a carboxytetramethylrhodamine (TAMRA), referred to as strand M, was encapsulated in the gate microdroplets to distinguish the microdroplets by fluorescence observation. Strand M had no relationship with the behaviors of the logic gate.

3.5 DNA solution preparation

All DNA strands used in this study (Table 1) were synthesized by Tsukuba Oligo Service, Japan. DNA stock solutions were prepared at 100 μM in TE buffer (10 mM Tris–HCl, pH 8.0, 1 mM EDTA). The gate was constructed by mixing 2 μL of the stock solutions of the necessary strands (T1–T3 for the AND gate, and S1–S3 for the OR gate), 3 μL of the stock solution of M, and 1 μL of 10× saline–sodium citrate (SSC) buffer, followed by incubation at 20°C for 20 min. The solutions for the input microdroplets contained 40 μM input DNA for the logical value 1 and no input DNA for the logical value 0.

4 Experimental results and discussion

Figures 4a, b show a sequence of bright-field images of transporting process of microdroplets. Four light spots generated at the position of the vertices of a 6.7-μm-sided square were assigned to individual microdroplets to trap. The spots were translated manually into 1.7-μm steps with the SLM. Two microdroplets were transported to the reaction position in conformity with the generated spot patterns. The microdroplets were controlled by optical manipulation in two dimensions. An XYZ stage was

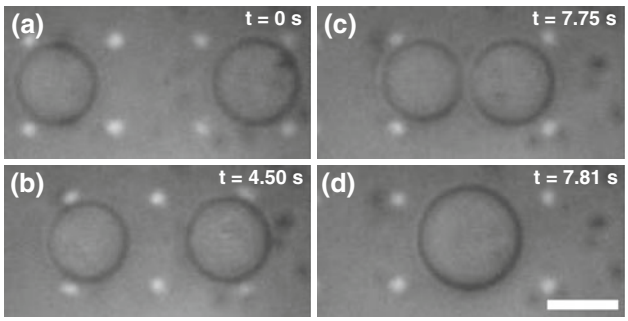

Fig. 4 Transportation and fusion of two microdroplets using light. **a**, **b** Microdroplets transported by shifting the square spot patterns. **c**–**d** Microdroplets contacted and fused using optical pressure forces. *Scale bar* 5 μm

employed to adjust the position along the optical axis (z) direction. In this experiment, some effects induced by light irradiation, for example heating the microdroplet contents, can be negligible because the microdroplets have low absorption efficiency for the laser beam used. Figures 4c, d show a sequence of bright-field images in the fusing process of microdroplets. Two spots were assigned to each of the microdroplets and were shifted to move the microdroplets closer. Immediately after contact with each other, two microdroplets were merged to form a larger microdroplet. The total optical power including 0th order light and holographic spots at the sample plane was 7.8 mW. The variation of the total optical power during translation was approximately constant because the spots were generated near the optical axis and the power losses due to vignetting was negligible. The optical pressure force which a microdroplet received from a single spot against the power was measured as 0.6–1.0 pN/mW (Ogura et al. 2011a).

It has been confirmed that the microdroplets can be merged with little leakage of the solution by this method (Ogura et al. 2011a). The optical manipulation of microdroplets with a spot-array pattern provides parallel and flexible control of the microdroplets because real-time generation of the desired optical pattern is achievable with light-controlling devices such as an SLM (Eriksen et al. 2002). This capability is valuable for adaptive control by designing appropriate light patterns to manipulate microdroplets according to the processing status.

To demonstrate operation of the logic gates, two kinds of microdroplets, one containing AND or OR logic gates (20 μM) and the other containing input DNAs (40 μM), were prepared and manipulated to be fused. The AND and OR gates were operated for every possible input combination, (0, 0), (1, 0), (0, 1) and (1, 1). Figure 5a shows bright-field images and fluorescence images captured before and after the AND operation for (1, 1) by using the cooled CCD. The fluorescence intensity of the

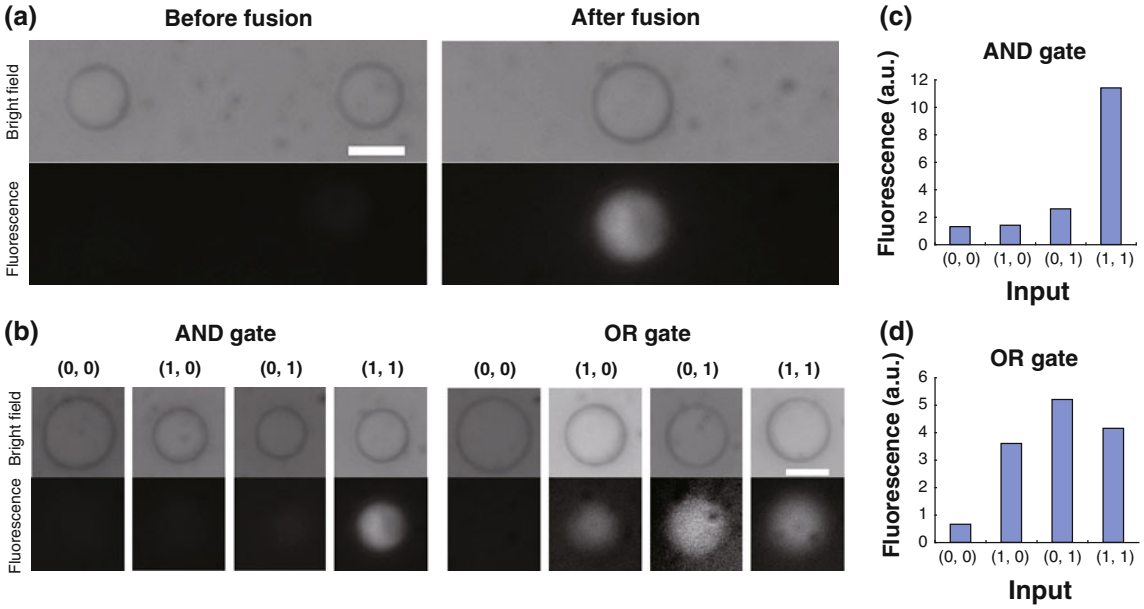

Fig. 5 Results of the logical operations with microdroplets. **a** Bright-field and fluorescence images captured during the AND operation for input (1, 1). The *left* microdroplet contains input DNA and the *right* contains the AND logic gate. **b** The fluorescence results of AND and OR operations for inputs (0, 0), (1, 0), (0, 1) and (1, 1). The bright-field (*upper*) and fluorescence (*lower*) images after the operation. Exposure time of the fluorescence images was 5 s. **c**, **d** Fluorescence intensity measured for logical operations of (**c**) AND and (**d**) OR. All *scale bars* 5 μm

microdroplet increased after fusion, which indicates that the result of the logic operation was 1. All results obtained from AND and OR operations are shown in Fig. 5b. Figures 5c, d show the increasing rates of the fluorescence intensity of the fused microdroplet measured after AND and OR operations for all input combinations. The relative intensity, R, was defined as $R = F/F_0$, where F and F_0 were the fluorescence intensities averaged over the area of the microdroplet and the gate microdroplet before the fusion. For AND operations, the relative intensity was high only when the input was (1, 1), indicating an output of 1. In contrast, when the input was (0, 0), (1, 0) or (0, 1), the fluorescence remained at a low level, indicating an output 0. The relative intensity of the microdroplet after operating the OR gate also agreed with the expected output of the OR operation: the intensity was low only when the input was (0, 0) and high in other cases. The result indicates that logic operations can be executed within a small volume by optical manipulation of microdroplets. The relative intensities representing output 1 were different between the AND gate and the OR gate. The fluorescence dye was quenched by a single quencher dye in the OR gate. In constant, two quencher dyes existed in the individual AND gates. As a result, the value of F_0 of the AND gate was lower than that of the OR gate, and therefore the intensities of the AND gates were higher than that of the OR gate microdroplets. The variation of the intensity output values was caused by difference of the size of the microdroplets. The amount of the gates encapsulated in a microdroplet depends on its size, and effected on the reaction efficiency and the fluorescent intensity of microdroplets. The fluorescence intensity depends on not only the logical results but also types of DNA logic operations, and a proper threshold should be selected under each condition. As a reference, when the threshold value T, is simply defined as $T = (O_1 + O_0)/2$, where O_1 and O_0 were the average of the relative intensity in the case of 1 output and 0 output in each gate, $T = 6.6$ in the AND gate and $T = 2.5$ in the OR gate, respectively. Using these threshold values, output 1 and 0 can be distinguished.

To confirm the advantage of miniaturizing a reaction volume by using microdroplets, we measured the time required for AND operations and investigated its dependence on the reaction volume. A microdroplet containing the AND gate (10 μM) and another microdroplet containing the input (1, 1) (10 μM) were fused to operate the gate in the merged microdroplet, whose volume was estimated to be 0.3 pL from its diameter. Figure 6a shows the time course of the fluorescence intensity of the microdroplet measured in intervals of 0.5 s. Some dispersion included in the measured values is due to low sensitivity of the camera used for the measurement. The time required for the fluorescence intensity to reach the equilibrium state was <2 s after the fusion in the microdroplet. Figure 6b shows the time course of the fluorescence intensity during the AND operation in a 50 μL cuvette. The operating time of more

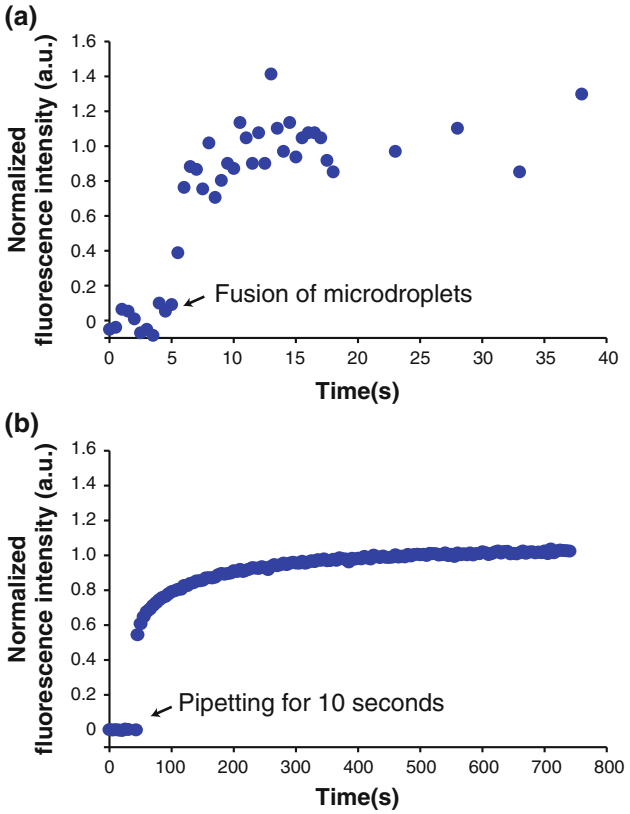

Fig. 6 Time courses of fluorescence intensities during the AND operation for input (1, 1) in **a** microdroplet and **b** cuvette. The time course of fluorescence intensity in the cuvette was obtained by the following procedure: five microlitres of stock solutions of T1, T2, T3 and 10 × SSC buffer in addition to 20 μL of TE buffer were mixed and incubated for 20 min at 20°C in a cuvette (5 × 5 mm) (JASCO, Japan) to fabricate the AND gate. A solution prepared by mixing 5 μL stock solutions of I1 and I2 was added to the AND-gate solution. After the mixture was pipetted for 10 s, the fluorescence intensity during the AND operation in the cuvette was measured every 5 s by using a spectrofluorometer (FP-6200) (JASCO, Japan)

than 300 s was required after pipetting for 10 s. This experimental result shows that the operation time is shortened by miniaturizing the reaction volume.

Mixing of the solutions within the microdroplet was achieved by molecular diffusion. The diffusion time, t, was approximated by $t = x^2/2D$, where x is the diffusion distance and D is the diffusion coefficient. The relationship indicates that the operation becomes faster as the reaction volume is reduced. The diffusion coefficient of DNA is reported to be 9.943×10^{-7} cm^2 s^{-1} (for 18-base-pair oligonucleotides) (Nkodo et al. 2001); therefore, the diffusion time of the DNAs in a microdroplet with a 10 μm diameter is estimated to be about 500 ms. A possible reason why the operation in the microdroplets required a second-scale time (2 s) in the experiment is that the reaction time is constrained by the time required for strand displacement. On the other hand, when the AND operation for the input (1, 1) was executed in a 50 μL volume without pipetting, the operation time was more than 4 h (data not shown). Although the operation time was shortened by pipetting (300 s), as shown in Fig. 6b, it was still more than that required by our proposed method (2 s). Rapid response of the gate was accomplished owing to rapid mixing by limiting the diffusion length to a micrometre scale.

We executed single 2-input- 1-output AND and OR operations in this study. Other gates, including NOT gates, can also be operated in the manner. For example, enzyme-free logic circuits proposed by Seeling can be applied straightforwardly (Seeling et al. 2006). In addition, complicated operations have been achieved by constructing a large DNA circuit that combines multiple DNA gates (Qian et al. 2011). By use of these DNA circuits, any logical operation including NOT, NAND, and NOR logical operations will be achieved based on optofluidic DNA computation. In the demonstrated DNA circuits, signals between the gates were cascaded using signal DNA diffusion, and the operation speed was a limiting factor in creating larger circuits. For example, a circuit consisting of 11 gates and accepting 6 inputs required 2 h to reach half-activation (Seeling et al. 2006). The optofluidic DNA computation method enables reduction in the operation time by limiting the diffusion length to a micrometre scale and thus contributes to improvement in the processing performance.

Compared to droplet control using flow in a microchannel, control speed of optical manipulation is low, which indicates throughput degradation (Teh et al. 2008). For example, linear flow rate in the flowing system is millimetres per second (Dittrich et al. 2006) and transportation velocity of optical manipulation is micrometres per second (Ogura et al. 2011b). However, the advantages of optical manipulation include a parallel, dynamic and reconfigurable control. The maximum number of microdroplets that can be manipulated simultaneously and controlled independently is estimated to be about 1,000 (Ogura et al. 2011a). These features of optofluidic DNA computation provide high potential in biological applications.

5 Conclusion

As a first demonstration of optofluidic DNA computation, we performed logic operations based on the DNA logic gate operation in a small volume by optical manipulation of microdroplets. We confirmed the feasibility of rapid operation by downsizing the reaction space to the micrometre scale. Many studies of DNA logic gates are based on sequence recognition and strand displacement, which were utilized in the gates. Our method can improve the

processing performance of DNA circuits composed of DNA gates. In addition, our method can achieve immense parallel processing power through the application of parallel optical manipulation and adaptive control. From this perspective, optofluidic DNA computation has high potential for analysis and control of biological systems.

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