Solution of a SAT Problem on a Photochemical DNA Computer

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(Received November 19, 2004; CL-041393)

The photochemical DNA computing via 5-carboxyvinyl-deoxyuridine ([cv]U) in anchor oligodeoxynucleotides (ODNs) in order to tether the multiple "DNA words" was demonstrated. A new MARK and UNMARK operation based on the [cv]U mediated reversible DNA photoligation has been developed for multiple-words DNA computing. The utility of this operation for DNA computing was demonstrated by solving a satisfiability problem (SAT problem) in which information was encoded in three tandem words.

The study about DNA computing was initiated in 1994 by Adleman[1] who focused attention on exceptional parallel process of DNA molecule and solved Hamiltonian path problem. Thereafter, various NP-complete problems were solved by enzymatic manipulation of DNA.[2–5] However, such enzymatic operation have some hurdle about the stability of enzyme and the limited condition in their use including the most suitable temperature and pH caused from the use of enzyme. On the contrary, the method of the photochemical manipulation avoiding the need for additional reagent is obvious. Particularly, photochemical ligation methods are useful for those situations in which chemical or enzyme mediated ligation is undesirable or unfeasible, for example inside a cell. Template directed reversible DNA photoligation via 5-carboxyvinyldeoxyuridine has already reported as a phototriggerd DNA manipulation and was able to create a branched ODNs at target site.[6] In this manipulation, the ligated ODN can be split site-selectively to regenerate the parent ODN by photo-irradiation at 312 nm (Figure 1). We report here the development about DNA computing using photochemical ligation of DNA.

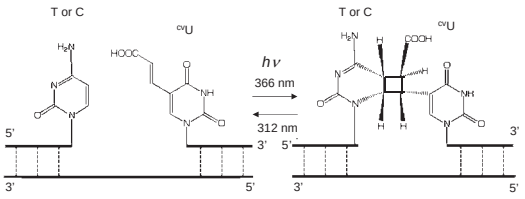

Figure 1. Template directed reversible DNA photoligation via [cv]U.

The DNA sequences in this study were shown in Table 1. Any information such as *x*, *y*, 1 (true) or 0 (false) was represented by three bases. The [cv]U was synthesized from 5-iodo-2′-deoxyuridine. [cv]U-containing anchor-ODN was immobilized and prepared according to the standard phosphoramidite chemistry on a controlled pore glass (CPG) surface with a DNA synthesizer. The answer-ODNs and template-ODNs were commercially synthesized (Hokkaido System Science Co, Hokkaido, Japan).

Table 1. Designed ODN sequence and information encoding scheme[a]

Variable	Sequence (5′–3′)	Boolean value	Sequence (5′–3′)
x	ATG	1	GGT
y	GCT	0	CAC
z	TGC		

answer [*xyz*]	Three-words ODN sequence (5′–3′)
111	ATGGGT-GCTGGT-TGCGGT
101	ATGGGT-GCTCAC-TGCGGTAA
011	ATGCAC-GCTGGT-TGCGGTAAAA
001	ATGCAC-GCTCAC-TGCGGTAAAAAA
110	ATGGGT-GCTGGT-TGCCACAAAAAAAA
100	ATGGGT-GCTCAC-TGCCACAAAAAAAAAA
010	ATGCAC-GCTGGT-TGCCACAAAAAAAAAAAA
000	ATGCAC-GCTCAC-TGCCACAAAAAAAAAAAAAA[b]

Variable	Boolean value	Template-ODN sequence (5′–3′)
x	1	GTCGTAACCCAT
x	0	GTCGTAGTGCAT
y	1	GTCGTAACCAGC
y	0	GTCGTAGTGAGC
z	1	GTCGTAACCGCA
z	0	GTCGTAGTGGCA

Anchor-ODN sequence (5′–3′)
[cv]UACGACSAAAAASAAAAA-CPG[c]

[a]Any information was represented by three bases, and answer-strands were composed of a combination of such three bases. [b]"A" series of 3′-tail were introduced to isolate peaks in Capillary Gel Electrophoresis (CGE) analysis. [c]"S" in the anchor-ODN describes hexaethyleneglycol, which separate the hybridizing sequence region from the solid support.

Those oligonucleotides were used without further purification.

The answer-strands "[111]", "[011]", "[110]", "[010]" were employed to calculate the logical Eq 1 called SAT problem.

$$(\bar{x} \vee z) \wedge (x \vee z) \wedge (x \vee \bar{z}) = 1 \qquad (1)$$

In this equation, variable *x*, *y*, and *z* are Boolean and can assume values of 0 (false) or 1 (true). There are three clauses separated by the logical AND operation "∧", which dictates that $(x \wedge z) = 1$ only if $x = z = 1$. Boolean variables within each clause are separated by the logical OR operation "∨", which dictates that $(x \vee z) = 0$ only if $x = z = 0$. $\bar{x}$ is the negative of *x*, which dictates that $x = 0$ if $x = 1$, and $\bar{x} = 1$ if $x = 0$. The SAT problem is to find whether there are values for the variables that simultaneously satisfy each clause in a given instance. Figure 2 shows our photochemical protocol for solution of a SAT problem. First,

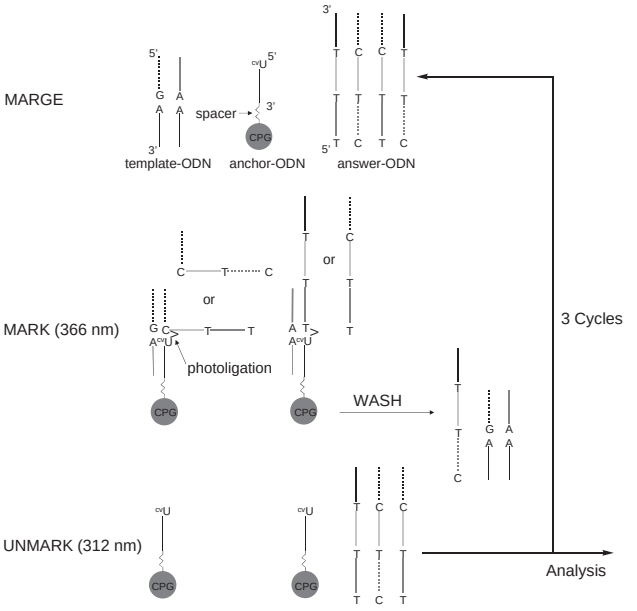

Figure 2. Overview of the photoligation-based approach to DNA computing.

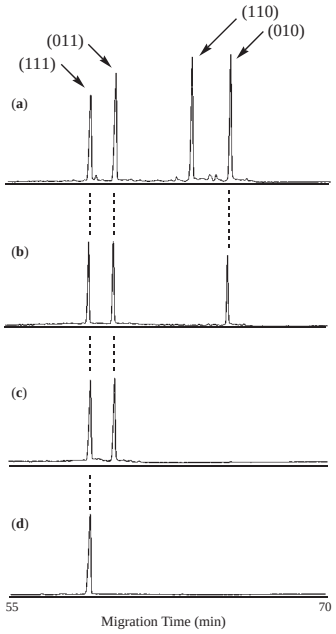

Figure 3. CGE analysis for each cycle. The peak intensity of the signals was normalized with strand [111]. (a) before calculation (b) after operation $(\bar{x} \vee z)$ (cycle 1) (c) after operation $(x \vee z)$ (cycle 2) (d) after final operation $(x \vee \bar{z})$ (cycle 3).

anchor-ODN, template-ODNs, and all answer-ODNs were mixed within a tube (MERGE operation[7]). After MERGE operation, matched answer-ODNs ware combined photochemically to the anchor-ODN under the 366-nm irradiation (MARK operation[7]). After MARK operation, denatured with urea to remove all the complements. Those denatured ODNs and nonreactive answer-ODNs were ablated by skimming the solution (WASH operation[7]). After WASH operation, the ligated answer-ODNs were detached from the anchor-ODN under the 312-nm irradiation (UNMARK operation[7]). The detached answer-ODNs were recovered to be used in next MARK operation. Solving each clause of the SAT problem requires one cycle of MERGE, MARK, WASH, and UNMARK, and 3 cycles were employed to solve Eq 1.

The experimental results corresponding to the process outlined below are shown in Figure 3. In cycle 1, answer-strands "[111]", "[011]", and "[010]" were marked (ligated photochemically to anchor-ODN in duplex structure) by complemental template-ODNs "$x = 0$", and "$z = 1$". Therefore, they remained after the WASH operation. In contrast, strand "[101]" was eliminated in the WASH operation. Answer-ODNs tethered to anchor-ODN were photosplit by the UNMARK operation to regenerate the answer-strands "[111]", "[011]", and "[010]" in 53% yield. In cycle 2, answer-strands "[111]", and "[011]" were similarly marked by complemental template-ODNs "$x = 1$", and "$z = 1$" and strand "[010]" was eliminated in the WASH operation. Answer-strands were obtained in 51% yield after UNMARK operation. In final cycle (cycle 3), only answer-strand "[111]" was marked by complemental template-ODN "$x = 1$", and "$z = 0$" and strand "[011]" was eliminated. After those three cycle of DNA computing, the left DNA molecule was answer-strand "[111]" corresponding to the correct answer for Eq 1 in 48% yield.

In this paper, a clear solution for SAT problem by DNA computing based on photochemical ligation of DNA "words" has been demonstrated. This photochemical computing method based on reversible photoligation will be a progressive manipulation for stagnant DNA computing based on enzyme and applied to solve more complicated mathematical problem. Moreover, this photochemical ligation method are versatile, and may find a myriad of application not only to a high-speed parallel gene analysis in biomedical field but also to high-capacity molecular memory in bioinformatic field.

References and Notes

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7 (MERGE) Anchor-ODN (80 μM), all answer-ODNs (20 μM) and template-ODNs required for calculation (50 μM) were mixed in an aqueous solution containing 1.5 M NaCl, and 50 mM cacodylate buffer, pH 7.0 at room temperature (MARK) The solution was incubated at 95 °C for 2 min, then cooled down to room temperature, and finally cooled to 0 °C with continuous temperature decrease at a rate of 1 °C per min, then irradiated with a transilluminator (366 nm) at 0 °C for 3 h. (WASH) To the solution mixture, 7 M Urea was added to denature the duplex. (UNMARK) The solution was irradiated with a transilluminator (312 nm) at room temperature for 1.5 min.

Published on the web (Advance View) February 12, 2005; DOI 10.1246/cl.2005.378