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Algorithmic Approach to Design Single Strand DNA-Based OR Logic Gate

Pradipta Roy✉

Department of Computer Science & Engineering, Swami Vivekananda Institute of Science & Technology, Dakshin Gobindapur P.S. Sonarpur, Kolkata, West Bengal, India

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ABSTRACT. In this paper a realistic algorithm for designing deoxyribozyme based logic gates was proposed. The algorithm was capable to provide desired output and maintain the law of logic gates that could be verified with their already proved truth table. The basic OR logic gate algorithm was designed. Significantly, oligonucleotide was utilized as input as well as in output so that they exposed the opportunity of connection between several computational components in the chemical solution to make bio-inspired circuit.

KEYWORDS. Single strand DNA; Oligonucleotide; Deoxyribozyme; Algorithm; Logic gate.

INTRODUCTION. The path breaking discovery by Adleman in 1994 leaded DNA computing as a new sphere of influence in the computer technology.[1] His experimentation showed the competence of DNA computing by solving Hamiltonian Directed Path Problem (HDPP) using DNA. After introducing that research on DNA computing, the topic got very much importance for the last two decades, as it was precious in marker based disease detection. Interestingly, it has been already reported that the cancerous cells could be detected with the help of DNA technology.[2] The DNA technology could be used as an unconventional method for lower time complexity, enormous parallelism, low power consumption, massive information storage capacity and also its reversibility features.[3] The development of basic circuit unit requires some molecular computation which results confirmation about cancerous cell detection. The basic gates AND, OR and NOT gate are fundamental module to design single strand DNA based logic design.[4] Nucleic acid has been used as an important material in the field of artificial biochemical circuit design due to its various enviable properties.[5] Different signals could be determined and corrected by nucleic acid sequences. For designing the biochemical circuits using DNA, some ancillary enzymes have been used already.[6, 7] Some inventive molecular devices or circuits have been developed based on performing molecular computations with structural properties of DNA such as hairpin.[8-12] Some simpler basic module such as AND gate, NOT gate, OR gate have been already projected for constructing large scale circuits.[13,14] Several digital logic circuits have been implemented with the strand displacement property of DNA to construct the circuit module to deal with information where the computation was performed chemically. This property was very constructive to generate easy but strong-and-stout circuit which could be computed rapidly.[15] Though DNA could be used in molecular computations, the biologists have been always very eager to discover correlation between how DNA could be used in such data processing.

✉ Corresponding author: P. Roy; *E-mail address*: **pradiptoroy@gmail.com**, *ORCiD*: **0000-0001-6169-5027**.

Indeed, new paradigm in the field of computer technology has been started from the momentous experiment using DNA by Adleman at the University of Southern California in 1994.[1] As he proposed, DNA could be used as an element of computational materials to solve HDPP related problems by devising nondeterministic approach to achieve the purpose.[1] Each and every vertex of the graph has been formed by the random order of DNA and oligonucleotide used to represent each edge. Since then, the era of DNA computing has been begun and quite a few Turing machines have been constructed yet after that of the first proposed one by Alan Turing in 1936.[16] It is a simple automatic machine for manipulating different symbols on a tape-strip by following some rules, which could be adapted to simulate any the algorithmic logic.[16] In 1997, Ogihara and Ray suggested the evaluation of Boolean circuit.[17] After that, a programmable molecular computing machine has been suggested to arrange in an orderly manner of enzymes and DNA molecules as a replacement for silicon microchips in 2002. Then, in 2004, a DNA computer was constructed in attachment with an input and output unit with the ability of diagnosis cancerous activity within a cell prescribing as an anti-cancer drug.[18] Further investigations yielded several other logic gates even in nano scale.[19-21] More specifically, Breaker and Joyce biologists discovered the notion of using deoxyribozyme in DNA-based applications.[22]

The first idea of deoxyribozyme based logic gates was proposed in 2002.[13] The structural design of AND, NOT and Ex-OR gates were projected with the help of 8-17 and E6 deoxyribozyme, in which a constructed deoxyribozyme based half adder was introduced in 2003.[23] The half adder was constructed with solution-phase array of three deoxyribozyme based logic gates. Besides, the enzyme-free nucleic acid logic circuit was proposed in 2006.[24] The structural blueprint of OR logic gate was devised by Roy et al. in 2012.[14] In an earlier reported experiment, an artificial nucleobase methoxybenzodeazaadenine (MDA) was used to developed DNA logic as an alternative approach.[25] In addition to the main theory-based constrain of this technology making it hard to be implemented, but this work has the potential for futuristic simulation work related with DNA logic gates implementation as a novel approach for further investigations.

METHODOLOGY. DNA is actually the building block of life playing as a crucial macromolecule of every living organism with affinity to inherit characteristics from its ancestor of the same species.[26] Structurally, DNA is compared with the staircase along with guardrail. This molecule has double strand-double spiral structure, in which each strand is a tiny part linking to other indistinguishable molecule to form nucleotide. A nucleotide comprises with phosphate group and a nitrogen containing base attached to the 5′-terminal and 3′-terminal of a 5-carbon sugar to form the DNA backbone.[27] Adenine (A), Guanine (G), Cytosine (C) and Thymine (T) are four different types of nitrogen bases that are available in DNA.[28-31] The DNA backbone chains are formed by hydrogen bond interactions between complementary nucleotides of two strands.[26] In normal mode, Adenine contributes to two hydrogen bond interactions with Thymine and vice-versa whereas Guanine contributes to three hydrogen bond interactions with Cytosine and vice-versa. When two complementary simple strands form a double strand following the above rule, it is said that they are hybridized or annealed.

Oligonucleotide is short chain of nucleic acid which is one of the vital resources in artificial biochemical engineering field.[32] Oligonucleotides are basically single stranded connected nucleotides, sometimes called single strand DNA. For further clarification of this work, definitions on single strand DNA structure were described here.

Definition 1: Single strand DNA sequence could be represented by four-letter alphabets. ssD = $ssd_1ssd_2ssd_3ssd_4\ldots\ldots ssd_k$; $ssd_i \in \{A, T, C, G\}$ and i = 1, 2,……, k.

Definition 2: In a single strand DNA structure, two types of base pairs are formed including A-T (or T-A) and G-C (or C-G) according to Watson-Crick model so called canonical base pairs.[33]

Definition 3: The base pair formed by i-th base and the j-th base is represented by (i, j), then the subset of set ssD = $\{(i, j); 1 \le i \le j \le n\}$ is called ssDNA structure by satisfying following conditions for canonical (i, j) base pair: $(i, j) \in ssD$, $(i', j') \in ssD$; if $i \le i' \le j \le j'$, then i=i'.

Those single stranded chains are able to anneal in the case of finding appropriate complementary nucleotide in the opposite strand. The reason behind the selection of the single stranded chains of oligonucleotide is

generally for input/output of DNA logic circuit could be formulated by formations of the chains through *in vitro* experiments. The output from could be achieved by the cleaved product of oligonucleotide and a phosphorescence/fluorescence emission could be occurred.

Definition 4: The oligonucleotide is a short chain polymer of nucleotides from two up to twenty. The oligonucleotide sequence is represented by ogN_i, where og is the oligonucleotide and N is the nucleotide and i = 1,……, k.

Desired output could be obtained from the selection of particular sequences of oligonucleotide required for input in complementary sequence of catalytic DNA, so called deoxyribozyme. They are not provocative reactor instead they hardly take any initiative in chemical reaction, in which intervention of enzymes are required. Deoxyribozyme is produced by *in vitro* process following the model of ribozyme, which could develop catalytic functions in the case of correct configuration during *in vitro* processes. Subsequently, they could catalyze the chemical reaction in contact with fluorophore-spacer-receptor, called substrate.

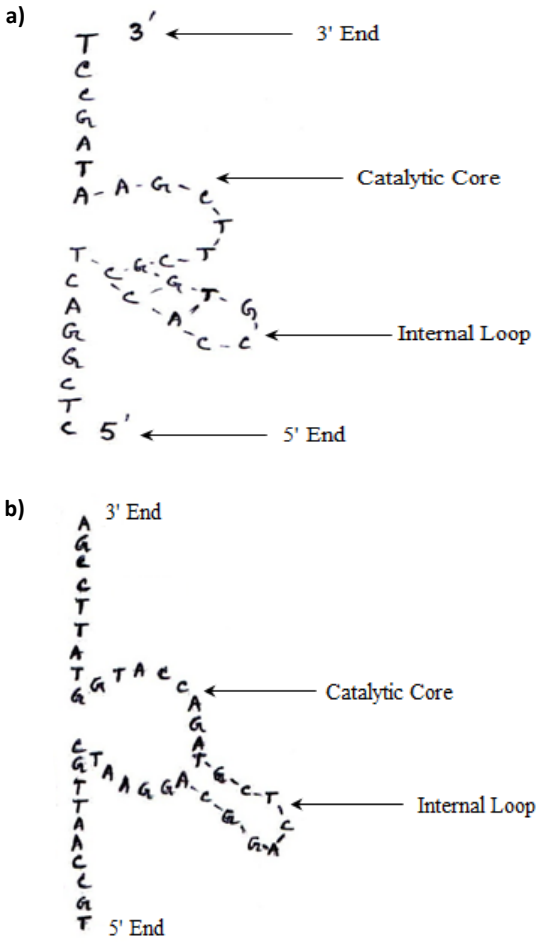

Fig. 1: a) 8-17 deoxyribozyme, b) E6 deoxyribozyme.

Mainly, two types of deoxyribozyme are produced in the laboratory to construct different logic gates such as 8-17 deoxyribozyme[34, 35] and E6 deoxyribozyme[22] as shown in Fig. 1. The 8-17 deoxyribozyme is composed of a catalytic core and a fixed internal loop, which could not be changed due to its strong hydrogen bond interaction between A-T and G-C bases. Conversely, E6 deoxyribozyme is comprised with a catalytic core along with an internal loop in which the internal loop is supposed to be changed by a preferred sequence of oligonucleotides in non-rigidity.

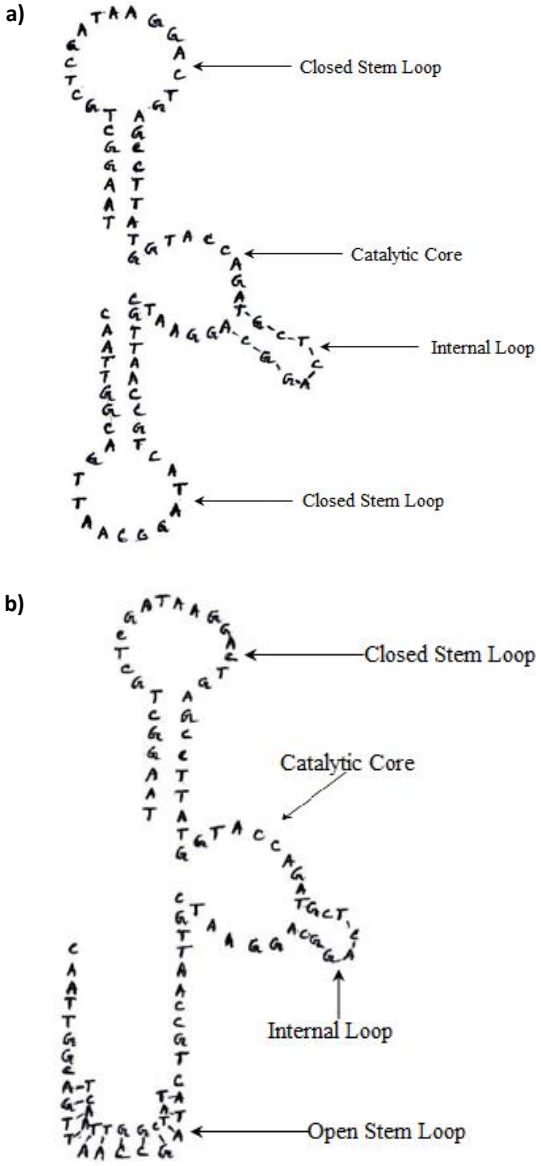

Fig. 2: a) Inactive form, b) active form.

The stem loop could be joined in the 3'-end and 5'-end of the limb or arm of the oligonucleotides innervating with the sequence of nucleotides precisely. The stem loops could be continued to couple with the arm of deoxyribozyme in complementary with non-mixable sequences of nucleotide with deoxyribozyme solution.

Such formation could be happened in the inactive form of oligonucleotide as shown in Fig. 2a. In contrast, the stem loops could be opened and annealed with the complementary sequence in the active form of mixable oligonucleotide in the chemical solution as shown in Fig. 2b.

The molecules could be divided into simpler molecules by breaking the chemical bond in cleaving method. In DNA-based logic gate, deoxyribozyme could split the substrate, which is basically a chain of nucleotide bases terminated by fluorescein donor (F) at 5'-terminal and tetremethylrhodamine acceptor (R) at 3'-terminal. The fluorescein donor (F) in the 5'-terminal part could be taken as output in the experiment. To fabricate DNA-based logic gates, deoxyribozymes are used as a catalyst, but they are not exactly so regarding persisting of a catalyst invariable before and after the chemical reaction. In DNA-based logic gates, if the input is "0", then the catalytic oligonucleotides do not amend, but if the input is "1", they become active by opening the stem loop. In this bio-inspired logic circuit, a short chain of oligonucleotide is treated as input.

```
Input: (i) Stem Loop1 (StemA) and Stem Loop2 (StemB);
       (ii) Input Sequence (IA) Less than LENGTH[StemA];
       (iii) Input Sequence (IB) Less than LENGTH[StemB];
       (iv) Substrate;

Output: cleaved product of initial substrate

Func: complement() provides the inverse sequence

      match() finds the patternin DNA sequence

OR()
{
   // Complementing the Input Sequence
   complement (IA, LENGTH(IA) );
   complement (IB, LENGTH(IB) );
   // Searching Complemented Input Sequence in Stem Loops
   flag1 = match(IA, StemA, LENGTH[IA], LENGTH[StemA]);
   flag2 = match(IB, StemB, LENGTH[IB], LENGTH[StemB]);
   if ((flag1 > 0) OR (flag2 > 0))
   {
      PRINT: OUTPUT;
      for i = 0 to position of (rA)
            PRINT: Substrate;
    }
    else
      PRINT: NO OUTPUT;
}
```

Algorithm I

RESULTS & DISCUSSION. The design of simple basic logic gate is necessary for building different combinational circuits. The basic logic gates could be used to construct large scale Boolean circuit. The construction of different elementary logic gates like AND, OR, NOT, XOR gate have been already proposed.[13,14] The AND and OR logic circuits along with NOT logic comprise the basic logic unit. Basic logic circuits are very much important regarding their assistance for constructing any kind of complex circuits. The OR logic function was simulated in this work (Algorithm I).

The initial substrate would be cleaved to provide our intended output when any one or both of the desired input sequences of oligonucleotide is blended within the chemical solution. Otherwise, when no input or desired input is applied to the solution, the initial substrate would not be cleaved resulting no phosphorescence/fluorescence emission. This process follows the OR logic gate as depicted in Table 1.

Table 1: Truth table of OR logic files.

Input		**Output**
I_B	I_A	O_F
0	0	0
0	1	1
1	0	1
1	1	1

Various catalytic ability of deoxyribozyme has been the computational power of deoxyribozyme. Two most popular deoxyribozyme for experimentation are 8-17 and E6. In deoxyribonucleotide framework, the cleavage occurs at the point of ribonucleotide (rA) of the substrate. It has been previously reported that the logic circuit could be represented in the variety of set theory approach. In this case, the conjunction AND process has been presented by intersection method. Subsequently, disjunction OR and negation NOT processes could be obtained by union and complement methods, respectively. Disjunction operation could be formulated by eq. (1).

$$O(\mathrm{F}) = sl \cup s \cup I = S_F \quad (1)$$

In eq. (1), *sl* represents deoxyribozyme with stem loop, *s* means substrate and I is the input and *O*(F) is the output oligonucleotide which emits fluorescein donor (F) attached in 5'-terminal as output.

The simulated output for input combination 00 is shown in Fig. 3. Here, the column 'combination' actually shows which input sequence is activated. According to the well-known truth table of digital logic design, no output for input combination 00 (Fig. 3).

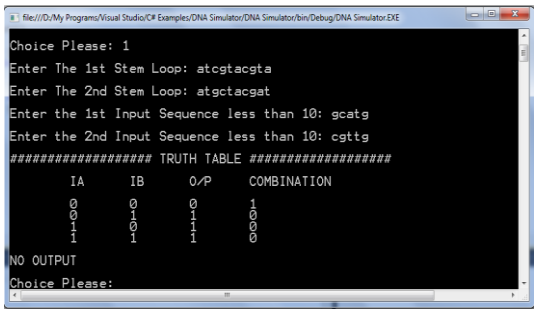

Fig. 3: Simulated output for input combination 00.

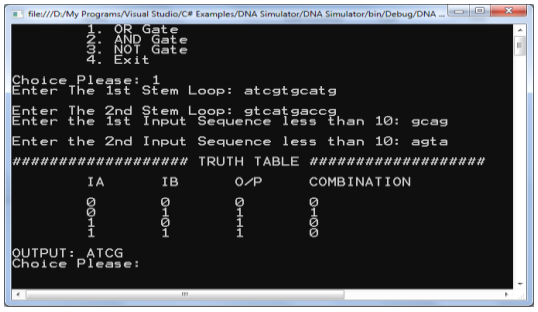

Fig. 4: Simulated output for input combination 01.

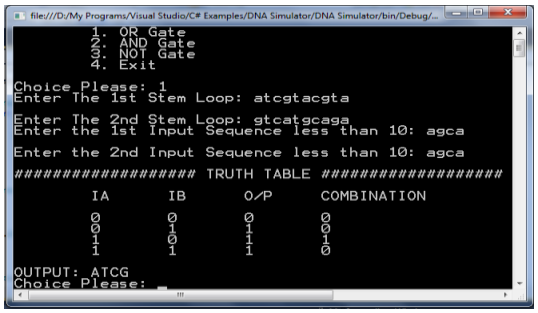

Fig. 5: Simulated output for input combination 10.

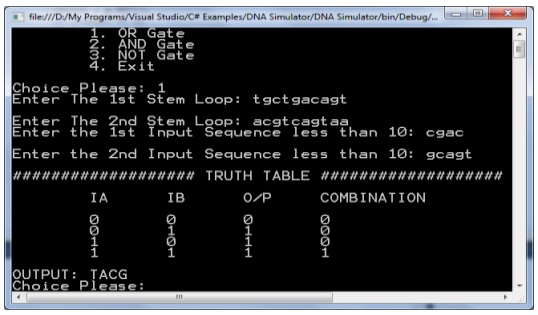

Fig. 6: Simulated output for input combination 11.

A deoxyribozyme based tool with the advent of the algorithm was designed here. The tool could be capable of taking the input according to the operator's choice. They might choose the deoxyribozyme according to their choice. The entire thing is customized. To formulate GUI tool based software, the algorithmic approach of designing the deoxyribozyme based logic gate was very crucial. The algorithm was very much supportive in terms of software designing. Details of such processes were exhibited in Figs. 3-6 to describe how the algorithm could work with the system. As indicated earlier, the column 'combination' actually shows which input sequence is activated. According to the well-known truth table of digital logic design, outputs were shown for the inputs despite input combination 00. Fig. 4 represented input combination 01, Fig. 5 represented input combination 10, and Fig. 6 represented input combination 11 and their corresponding outputs.

CONCLUSION. Intersection (AND), union (OR) and complement (NOT) are the fundamental building block of logic gates; all other combinations could be achieved by those operations. On the other hand, with the help of this algorithm, the construction of universal logic gates could be made. Universal logic gates facilitate the articulation of any Boolean function. The algorithm was expressed by following *in vitro* process of making the deoxyribozyme based logic circuit. This algorithm was very much helpful for designing tool that could analyze the DNA circuit very efficiently. Based on the input combinations, specific outputs were achieve.

DISCLOSURE STATEMENT. The author(s) did not report any potential conflict of interest.

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