Current Trends in Biotechnology and Pharmacy
Vol. 11 (2) 160-166 April 2017, ISSN 0973-8916 (Print), 2230-7303 (Online)


# Algorithm to Simulate a Chemically Induced DNA Logic Gate and Boolean Circuit

**Kuntala Boruah*, Rashmi Deka and Jiten Ch Dutta**
[1]Department of Electronics and Communication Engg.
Tezpur University, Tezpur - 784028, Assam, India
*For Correspondence - kuntala17@gmail.com

**Abstract**

A simple proof-of-principle type of simulation of chemically implemented logic gate is proposed in this paper using the structural switching of single stranded DNA strand from i-motif to hairpin and vice versa which is triggered by regulating $H^+$ and copper (II) ions. The advantage of such chemically induced gates lies in its fast response time, controllability and reusability feature. Later on this simulation process is expressed in the form of algorithm to evaluate AND-OR Boolean circuit.

**Key words:** DNA, AND gate, OR gate, Boolean Circuit.

## Introduction

Watson and Crick claimed novel prize in 1953 for the discovery of the double helical structure of DNA. For ages DNA is known as primary genetic material responsible for transmitting genetic information from one generation to another until Adleman(1), for the first time recognized the information processing property of DNA and demonstrated the first ever DNA synthetic computer by solving an instance of HPP. With time, enormous numbers of research are reported to employ DNA computing approach for solve several diverse fields of problems. DNA Boolean circuit simulation draws most of the interest and efforts. Ogihara and Ray (2,3) proposed the first DNA system that can simulate bounded Boolean circuit with complexity proportional to size of circuit. Since then several theoretical and experimental models and algorithms have been proposed. Analogous to silicon logic gate, molecular logic gate is expected to act as fundamental for biological or molecular computers (4)-(14).However the efficiency of most of such model is limited by involving too many error prone and time consuming biochemical processes. Recently secondary structure of DNA such as G-quadruplex and i-motif structure finds their way into several gate simulation models due to their unique properties such as highly specific binding properties, polymorphic versatility, and self assembly (15-19). There are several models reported where i-Motif structure coexisted with G-quadruplex but such models experienced the set back in terms of its complex maintenance and high cost (20,21). In few models G-quadruplex structure is solely used (22) whereas in some other models i-motif structure is solely used in construction of gate designing (23,24). Yunhua et al.(24) demonstrated DNA logic gates using only i-motif structural induction in response to the presence of $H^+$, $Ag^+$, and $I^-$ as inputs. This simple technology has potential to simulate the functionality of OR and INHIBIT gate.

Henry Albert Day et al. (25) published the switchability of pH induced i-motif structure to hairpin and vice-versa. During the experiment they initially induced i-motif structure in human telomeric sequence at pH 5.5(folding time of 100 milli seconds) which was altered to hairpin structure by adding $Cu^{2+}$ at room temperature without changing the pH . The folding time of i-motif structure to hairpin on adding $Cu^{2+}$ was estimated to be 44 $\pm$ 2 seconds. Further they

successfully reverse the hairpin structure to i-motif structure by adding EDTA. The total time span of a complete cycle of folding or unfolding is 100 seconds only.

In this application based paper, it is proposed that AND-OR gate can be chemically induced by using the switching property proposed by H.A Day and his group. The author proposed an algorithm to simulate logic gates and evaluation of Boolean circuit using secondary structural switching of C-rich chain of DNA. Instead of encoding the gate strand and the input strands in the form of DNA sequence, in this paper the ions and pH are programmed and controlled. It is expected that this model have several advantages such as cost effectiveness, fast response time, reusability and easy implementation.

**Preliminaries**

***DNA i-motif :*** For decades it's been believed that DNA remain in only B-form double helical structure as proposed by Watson and Crick but after extensive studies in following years it is well established that DNA can be found to be in several different secondary structures such as in A and Z forms, triplexes, three and four way junctions and quadruplexes. i-motif or i-tetraplex structure is one of such secondary structures of DNA which recently gains lot of interests. It is a four stranded structure formed by intercalating two pair duplexes of anti parallel orientation which are held together via hydrogen bond between cytosine$^{+}$–cytosine base pairs. There are several ways to enhance the formation of i-motif such as acidic pH of the solution or at neutral pH with the presence of certain ions like $Ag^{+}$ (27) etc. In human genome i-motif sequence present as complementary sequence of G-quadruplex forming sequence such as human telomeric i-motif sequence (hTeloC)(26). Several research works are reported expecting to use i-motif structures for anticancer drug development and gene regulation (28,29) and several other applications such as construction of biosensors(pH sensors), logic circuits, nanomachines and functional materials like proton-fuelled i-motif nanomotor, DNA ''bipedal walkers''.

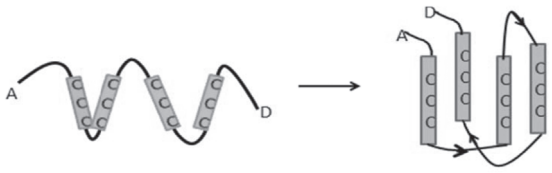


**Fig. 1:** Switching of C-rich sequence to i-motif structure

***DNA hairpin*** *:* DNA hairpin structure is obtained when two self complementary segment in a single stranded DNA fold itself to self-hybridize. The resulting structure consists of two parts: stem part and the loop part. Stem part are the two self complementary sequences and the loop portion is the sequence which doesn't take part in the hybridization. The stem-loop structure owes its stability to the length, involvement of G-C pairs, and number of mismatches in the stem. Hairpin structure finds its application in several biomedical and nano-technology field.

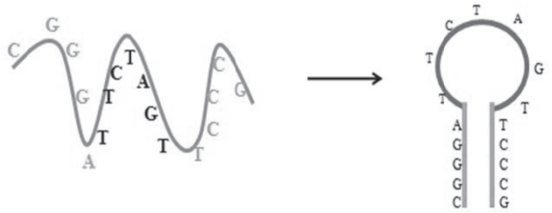

**Fig. 2.** Single stranded to hairpin structure.

***Logic Gate and Boolean circuit simulation:*** In a Boolean circuit, computational units which are responsible for carrying out information processing are called gates, connected to each other by a network of inputs and outputs. The output processing of gates are based on the present inputs available at that moment and don't have any memory about the past. The size and the depth of the circuit are the standards to measure the complexity of any circuit. Boolean circuit can be categorized in three types depending on the inputs and outputs associated:

- Unbounded fan-in Boolean circuit: No limitation to the numbers of inputs to both AND-OR gates.

- Semi-unbounded fan-in Boolean circuit: AND gate is limited to maximum of two inputs and no limitation to the numbers of inputs to OR gate.
- Bounded fan-in Boolean circuit: Both AND and OR gates can have maximum of two inputs. In this paper a Bounded fan-in Boolean circuit is proposed.

***i. AND gate simulation :*** AND gate evaluates 1 if all of its inputs are true otherwise it gives output as 0. The functionality of AND gate can be considered as serial connection. In this paper theoretic realization of AND gate is demonstrated at molecular level by regulating $H^+$ and $Cu^{2+}$ ($CuCl_2$) content. The entire process can be represented in the form of an algorithm (illustrated in Fig 3):

```
AND_operator (main_strand, T 1)
        {
T 1•! T 1 U main_strand;
       if (X1 = =0)
          {
          no titration of H+ to T1; //no change in
the structure of main_strand
           if (X2==0 || X2==1)
            No Cu2+ is added; // no change in the
structure of main_strand
           Output =0;
           }
            else
           if (X1==1)
           {
           Titrate H+ to T1; // main_strand change
to i-motif structure
            if (X2= =1)
               add Cu2+ to T1; // i-motif structure
change to hairpin structure;
            Output =1;
            else
          don't add Cu2+ to T1;// No change in the
i-motif structure;
            Output =0;
            }
            }
```

**Fig. 3.** Algorithm for AND gate

In the above algorithm the main_strand is the DNA strand( 5'-TAA-CCC-TAA-CCC-TAA-CCC-TAA-CCC-3') upon which all structural changes are observed, depending on the inputs (either $H^+$ or $Cu^{2+}$ or both). $T_1$ is the test tube where the reactions are carried out. The output is read as 1 when the structure of main_strand attain the hairpin shape which happens only when both the inputs are present and in any other case the structure of main_strand remains in either linear strand or in i-motif structure which is read as output 0 (illustrated in Fig 4.).

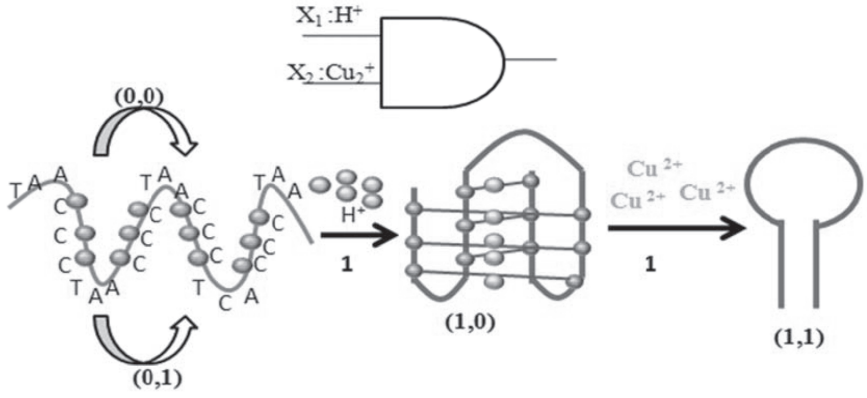


**Fig. 4.** Demonstration of AND gate.

**Table 1:** Two input AND gate

| | | | | | |
|---|---|---|---|---|---|
| $X_1$ | $H^+$ | 0 | 0 | 1 | 1 |
| $X_2$ | $Cu^{2+}$ | 0 | 1 | 0 | 1 |
| Output | | 0 | 0 | 0 | 1 |

***OR gate simulation :*** OR gate evaluates to 1 if any of its inputs are true otherwise as 0. The functionality of OR gate is like parallel connection. Unlike AND gate where $H^+$ and $Cu^{2+}$ acts as inputs, OR gate simulation is realized regulating only $H^+$ in the test tube. The entire process can be represented in the form of an algorithm (illustrated in Fig 5):

ORgate_operation (main_strand, $T_1$)
{
$T_1$•! $T_1$ U main_strand;
if ($X_1$==1 || $X_2$==1|| $X_1$==1&& $X_2$==1)
Titrate $H^+$ to $T_1$;//main_strand change to i-motif structure
Output=1;
Else
No $H^+$ is titrated to $T_1$;// no change to main_strand
Output=0;
}

**Fig 5.** Algorithm for OR gate

Main_strand is a C-rich strand having potential to attain i-motif structure (5'-TAA-CCC-TAA-CCC-TAA-CCC-TAA-CCC-3'). When $H^+$ is added to a test tube containing main_strand the pH of the solution changed to slight acidic and hence i-motif structure is obtained. The output is read as 1 in case of this molecular OR gate when the structure of main_strand attains the i-motif structure, which happens when either of the input is present (illustrated in Fig 6.).

**Table 2:** Two input OR gate

| | | | | | |
|---|---|---|---|---|---|
| $X_1$ | $H^+$ | 0 | 0 | 1 | 1 |
| $X_2$ | $H^+$ | 0 | 1 | 0 | 1 |
| Output | | 0 | 1 | 1 | 1 |

***iii. Boolean Circuit Evaluation :*** Fig 7. illustrated a diagram of a three leveled Boolean circuit with level 0 consists of inputs, level 1 consists of intermediate gates (AND and OR) and level 2 has AND gate. Any Boolean circuit can be visualized as a directed acyclic graph with all the gates as nodes connected to each other in such a way that the output of one level serves as input to the higher level. The algorithm to emulate a Boolean circuit is shown in Fig 8.

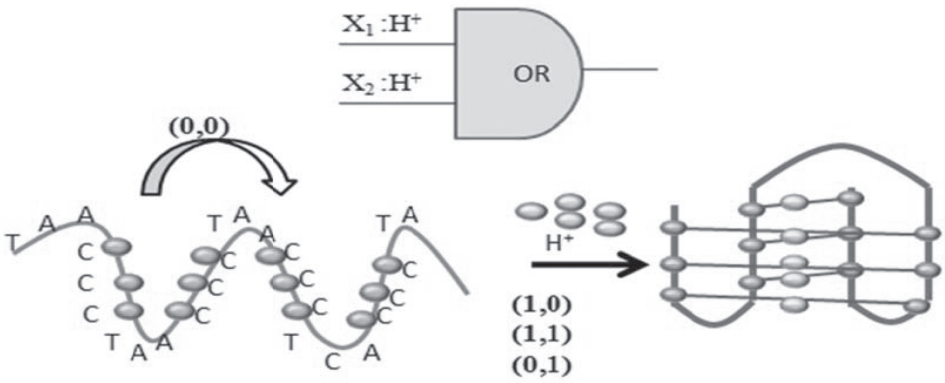


**Fig 6.** Demonstration of OR gate.

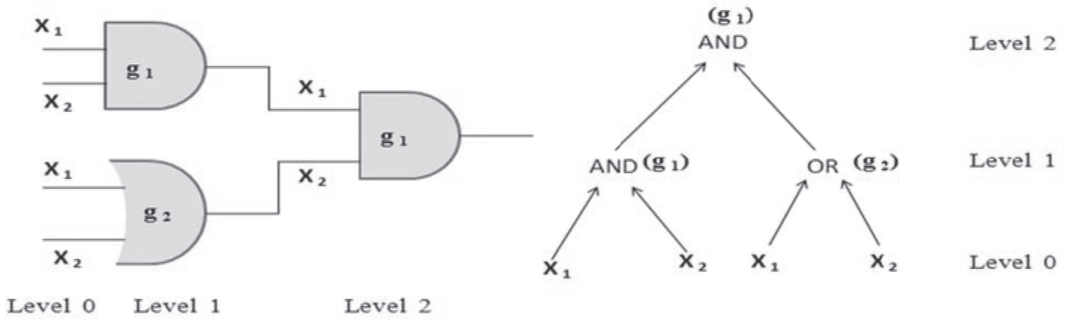


**Fig 7.** Instance of a AND-OR Boolean circuit.

```
Boolean_operator (main_strand,T1)
        for j=1 to j=level_max
              for k=1 to kÂ=gate_max
                if (gk==AND)
                  AND_operator(main_strand,T1);
                     if(gk==OR)
                  ORgate_operation(main_strand,T1);
              END for
        END for
```

Fig 8. Algorithm for AND-OR Boolean circuit

As the time incurred for each cycle of switching is only a few 100 seconds [25], it can be concluded that the proposed logic gate has fast response time. Similarly the model is reusable as several cycles of switching are possible for same strand of DNA as the linear strand can be restored every time by controlling the amount and concentration of pH, $Cu^{2+}$ or EDTA in the solution.

The model exploits the potential of three different structural outputs (linear, i-motif, hairpin) on the basis of pH condition and cationic concentration in the solution which provide a new insight to design DNA logic gate and Boolean circuits.

## Conclusion

In this paper a new gate design strategy is proposed to simulate AND and OR gate individually as well as to evaluate any AND-OR Boolean circuit by controlling $H^+$ and/or $Cu^{2+}$. The conformational structural change of C-rich DNA strand to i-motif structure and hairpin structure is utilized throughout the operations. The advantage of such chemically induced gates lies in its fast response time, controllability and reusability feature. Also the model offers a great potential in designing several nano machines as three structural outputs are possible using same strand of DNA. However this model lacks the feature of full automation and parallelism.

## References

1. Adleman, L. (1994). Molecular computation of solutions to combinatorial problems, Nature, 369: 40.
2. Ogihara, M and Ray, A. (1996). Simulating Boolean circuits on a DNA computer, Technical Report 631, University of Rochester. UK., 33-35.
3. Ogihara, M and Ray, A. (1999). Simulating Boolean circuits on a DNA computer, Algorithmica, 98, 725–730.
4. Ahrabian, H., Ganjtabesh, M. and Nowzari-Dalini, A. (2005). DNA algorithm for an unbounded fan-in Boolean circuit, BioSystems,82,52–60.
5. Amos, M., Dunne, P. and Gibbons, A. (1997). DNA simulation of Boolean circuits, Proceedings of 3rd Annual Genetic Programming Conference, 1–8.
6. Frezza, B.M., Cockroft, S.L. and Ghadiri, M.R. (2007). Modular Multi-Level Circuits

from Immobilized DNA-Based Logic Gate, J.Am.Chem.Soc.,129,14875–14879.

7. Genot, A.J. , Bath, J. and Turberfield, A. J. (2011). Reversible logic circuits made of DNA, J. Am. Chem. Soc., 133,20080–20083.

8. Goel, A. and Morteza, I. (2011). A renewable, modular, and time-responsive DNA circuit, Natural Computing, Springer, 10, 467-485.

9. Li, W., Yang, Y. , Yan, H. and Liu , Y. (2013). Three-input majority logic gate and multiple input logic circuit based on DNA strand displacement, Nano letters, 13, 2980-2988.

10. Li, W. , Zhang, F., Yan , H. and Liu, Y. (2016). DNA based arithmetic function: a half adder based on DNA strand displacement, Nanoscale, 8, 3775–3784.

11. Liu, W., Shi, X., Zhang, S., Liu, X. and Xu, J. (2004). A new DNA computing model for the NAND gate based on induced hairpin formation, BioSystems, 77,87–92.

12. Park, K.S., Jung, C. and Park, H.G. (2010). "Illusionary" Polymerase Activity Triggered by Metal Ions: Use for Molecular Logic-Gate Operations, Angew. Chemie - Int. Ed., 49, 9757–9760.

13. Shapiro,E. and Gil , B. (2007). Biotechnology: Logic goes in vitro, Nature nanotechnology, 2, 84-85.

14. Zoraida, B.S.E., Arock, M., Ronald, B.S.M. and Ponalagusamy, R.(2009). A novel generalized design methodology and realization of Boolean operations using DNA, BioSystems, 97, 146–153.

15. Parkinson, G.N., Lee, M.P. and Neidle, S. (2002). Crystal structure of parallel quadruplexes from human telomeric DNA, Nature, 417, 876.

16. Karsisiotis, A. I., Hessari, N. M. A., Novellino, E., Spada, G. P., Randazzo, A. and Webba da Silva, M. (2011). Topological Characterization of Nucleic Acid G Quadruplexes by UV Absorption and Circular Dichroism, Angewandte Chemie International Edition, 50:45, 10645-10648.

17. Liu, D. and Balasubramanian, S. (2003). A Proton Fuelled DNA Nanomachine, Angewandte Chemie International Edition, 42:46, 5734-5736.

18. Liu, D., Bruckbauer, A., Abell, C., Balasubramanian, S., Kang, D. J., Klenerman, D. and Zhou, D. (2006). A reversible pH-driven DNA nanoswitch array, Journal of the American Chemical Society, 128:6, 2067-2071.

19. Leroy, J. L., Guéron, M., Mergny, J. L. and Hélène, C. (1994). Intramolecular folding of a fragment of the cytosine-rich strand of telomeric DNA into an i-motif, Nucleic acids research, 22:9, 1600-1606.

20. Miyoshi, D., Inoue, M. and Sugimoto, N. (2006). DNA logic gates based on structural polymorphism of telomere DNA molecules responding to chemical input signals, Angewandte Chemie International Edition, 45:46, 7716-7719.

21. Zhou, J., Amrane, S., Korkut, D. N., Bourdoncle, A., He, H. Z., Ma, D. L. and Mergny, J. L. (2013). Combination of i Motif and G Quadruplex Structures within the Same Strand: Formation and Application, Angewandte Chemie International Edition, 52:30, 7742-7746.

22. Bhowmik, S., Das, R. N., Parasar, B. and Dash, J. (2013). pH dependent multifunctional and multiply-configurable logic gate systems based on small molecule G-quadruplex DNA recognition, Chemical Communications, 49:18, 1817-1819.

23. Ma, D.L., Kwan, M.H.T., Chan, D.S.H., Lee, P., Yang, H., Ma, V.P.Y., Bai, L.P., Jiang, Z.H. and Leung, C.H., (2011). Crystal violet as a fluorescent switch-on probe for i-motif: Label-free DNA-based logic gate, Analyst, 136:13, 2692-2696.

24. Shi, Y., Sun, H., Xiang, J., Chen, H., Yang, Q., Guan, A. and Tang, Y. 2014: Construction of DNA logic gates utilizing a H+/Ag+induced i-motif structure. Chemical Communications, 50:97, 15385-15388.

25. Day, H. A., Wright, E. P., MacDonald, C. J., Gates, A. J. and Waller, Z. A. E. (2015). Reversible DNA i-motif to hairpin switching induced by copper (ii) cations, Chemical Communications, 51:74, 14099-14102.

26. Amato, J., Iaccarino, N., Randazzo, A., Novellino, E. and Pagano, B. (2014). Noncanonical DNA Secondary Structures as Drug Targets: the Prospect of the i Motif, ChemMedChem, 9:9, 2026-2030.

27. Day, H. A., Camille, H. and Zoë A.E. W. (2013). Silver cations fold i-motif at neutral pH, Chemical Communications, 49, 7696-7698.

28. Kendrick, S., Kang, H.J., Alam, M.P., Madathil, M.M., Agrawal, P., Gokhale, V., Yang, D., Hecht, S.M. and Hurley, L.H. (2014). The dynamic character of the BCL2 promoter i-motif provides a mechanism for modulation of gene expression by compounds that bind selectively to the alternative DNA hairpin structure, Journal of the American Chemical Society, 136:11, 4161-4171.

29. Roy, B., Talukder, P., Kang, H.J., Tsuen, S.S., Alam, M.P., Hurley, L.H. and Hecht, S.M., (2016). Interaction of Individual Structural Domains of hnRNP LL with the BCL2 Promoter i-Motif DNA. Journal of the American Chemical Society, 138:34, 10950-10962.