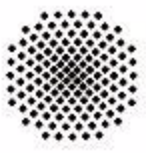
July 2002

Logic Gates made with DNA

Maria Belen Canadas Ruiz-Perez
Work supervised by Dr. Arnaud Virazel

Innovative Computer Architectures and Concepts Seminar



Universität Stuttgart

Abstract: The first step to construct molecular computational systems is to be able to develop simple units. The possibility of making logic gates with DNA (DeoxyriboNucleic Acid) means that we are not so far to reach this objective. NOT, AND and XOR gates have been constructed with deoxyribozyme (a special kind of DNA). The inputs and the output of these gates have the same nature (they are oligonucleotides), this is why it is reasonable thinking about the interconnection of these basic elements.

Index

1 Introduction

In 1994 the Adleman´s experiment [Adl94] opened a new world of possibilities in computing. He used DNA to solve the Hamiltonian path problem. It was a groundbreaking work that showed a new choice to avoid the limitations of the silicon technology. But what has happened after Adleman? How is now the state of the DNA computing?

One of the factors that helped the development of the molecular computing as an alternative to the silicon technology was the wide knowledge of the DNA that has been developed all through decades of studies. Biologist dealt with DNA and the events related with it before anybody could imagine the links between DNA and data processing. Nowadays, researches in the field of DNA computing take advantage of this knowledge and use the chemical reactions well known by biologists. Then progresses in biology lead to progresses in molecular computing.

In the last years, there have been a lot of advances in DNA computing [Lew02]. It is possible to solve definite complicated problems in a time considerably smaller than that spent by using a convencional silicon computer. DNA computing seems to be more useful now than at the beginning in solving such huge problems, intractable by the classical computing. The main advantages of molecular computing versus silicon computing are the possibility of executing several processes in parallel, the low power consumption and the high speed of the molecular events. If we would be able to manage these advantages, we will find an adequate field of application of DNA computing.

One of the possible applications of molecular computing that is being taken into account is the construction of molecular systems to detect diseases. These systems would be platforms able to compute input signals, thus recognizing markers of diseases. The first step consists on developing basic binary devices with DNA, for example, logic gates. One of the last ideas related to this field is the deoxyribozyme-based logic gates [Sto01]. Once more, a discovery in biology as the deoxyribozyme (catalytic DNA) [Bre95] produces an application in computing. That is the topic that will be discussed in this paper.

In the first part, the biological and chemical basic knowledge to understand the molecular processes involved will be clarified. In the second part, the achievement of the computation will be explained, establishing similarities between the behaviour of molecular and binary gates. Next, a simple explanation of the detection methods of the output will be done. On the other hand, not everything are advantages in the use of these structures. Afterwards, a discussion will be finally opened about the advantages, disadvantages, possibilities and impossibilities of the deoxyribozyme-based logic gates. Finally, a summary and a short overview about the future of this elements and the DNA computing in general will be discussed paying special attention in the evolution of the DNA computing research .

2 Rudiments of biology

Before dealing with the operation of the deoxyribozyme-based logic gates, it is necessary raising some basic concepts related to biology. What is deoxyribozyme? Why deoxyribozyme versus normal DNA? What are oligonucleotides? Why could oligonucleotides be used as inputs and outputs?

2.1 DNA

DNA is the way the nature storages information from one generation to the following of the same species. In the structural context, DNA is normally a double stranded macromolecule in double helix (**Fig. 1**). Each strand of DNA is a polymer formed by several monomer units called nucleotides.

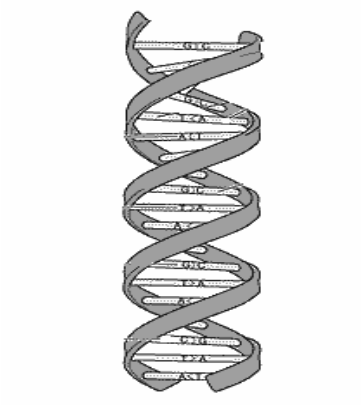


Figure 1: DNA double helix

A nucleotide consists of a 5-carbon sugar (deoxyribose), a nitrogen containing base attached to the sugar, and a phosphate group. The first letter of the bases gives the name to the nucleotides. There are four bases and therefore four nucleotides: adenine (*A*), guanine (*G*), cytosine (*C*) and thymine (*T*). The carbon atoms of the deoxyribose are numbered 1', 2', 3', 4', and 5'. The hydroxyl groups on the 5' and 3' carbons link to the phosphate groups to form the DNA backbone (**Fig. 2 b)**).

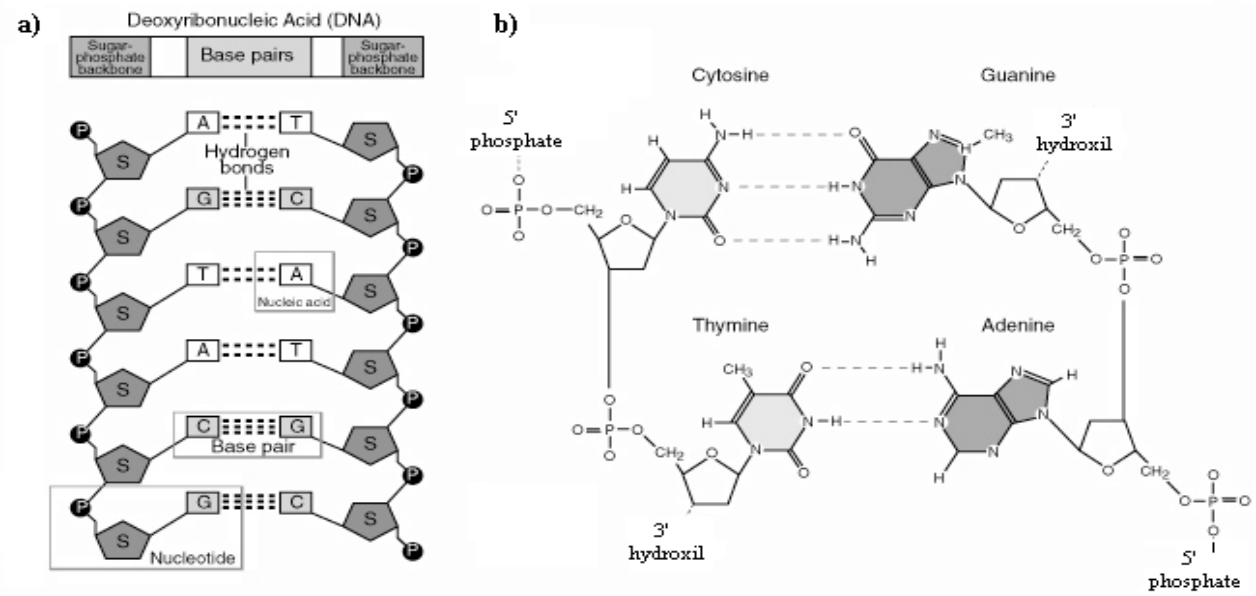


Figure 2: a) bonds in a double strand chain of DNA
b) hydrogen bonds between complementary nucleotides and bonds between nucleotides in the same strand

One DNA strand is an alternating backbone of deoxyribose and phosphodieser groups that has a polarity (direction) defined from 5' to 3'.

The two polynucleotide chains remain together by hydrogen bonds between nucleotides with complementary bases, one of them in one strand and the complementary in the opposite strand. *A* establishes two hydrogen bonds only with *T. G* establishes three hydrogen bonds only with *C* (**Fig. 2 a)**) [Wat53]. When two complementary simple strands form a double strand following this rule, it is said that they hibridize or anneal.

2.2 Oligonucleotides

An oligonucletide is a short chain of nucleic acid, a set of nucleotides joined in a single strand. These chains are able to anneal with the complementary sequence of nucleotides. There are several reasons to choose oligonucleotides as inputs and output of these logic gates. Some of these reasons are related to the objective of the project, being able to construct a computational molecular system to detect diseases. They are not important for us because they are not related with the functional processes of the logic gates. Another one is the possibility of taking advantage of the existing knowledge about the stability and intracellular structure of the oligonucleotides. And a practical reason is that we are able to produce a spe cific oligonucleotide easily.

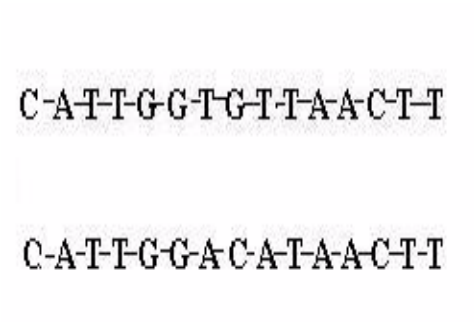


Figure 3: input sequence of nucleotides

Our inputs (**Fig. 3**) have a specific sequence of nucleotides which is the complementary sequence of a certain part of the deoxyribozyme, producing the desired effect that will be explained in part 3.

The output (**Fig. 4**) is a cleaved product oligonucleotide resulting from the cleaving of a initial substrate whose structure will be explained in part 4.

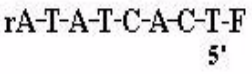


Figure 4: output sequence of nucleotides

The advantage of using inputs and output of the same nature is that the output of one gate can be used as input of another gate permitting the connection of gates to make a system.

2.3 Catalyst

Catalysts are chemical entities which participate in chemical reactions by making variations in other chemical entities possible, or by accelerating such reactions. By definition, a

catalyst is recovered intact after the complete reaction has taken place. In other words, catalysts permit other components to react between them, but do not change themselves.

The enzymes are catalyst; they are present in the reactions that involved DNA helping the events to occur. Until now, the proposed models in DNA computing were based in the well-known action of the enzymes over the DNA strands. But here a new model is explained which is based in a new catalyst: catalytic DNA or deoxyribozyme.

2.4 Deoxyribozyme

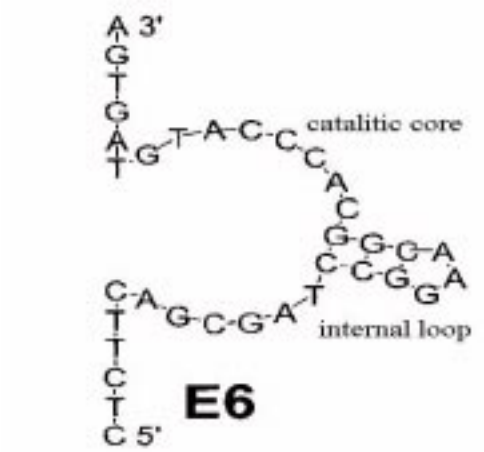


Figure 5: deoxyribozyme E6

Normal structure of DNA is not able to provoke reactions alone, it is necessary the intervention of an enzyme. For example, to clone DNA the action of the enzyme called helicase to melt the double strand chain is necessary. But DNA can develop catalytic functions if it is configured in the correct way.

This catalytic DNA is called deoxyribozyme. The deoxyribozymes are special structures of oligonucleotides configured in such a way that in contact with a fixed substrate, they catalyze a chemical reaction.

The deoxyribozyme is not present in the nature. It was created in a laboratory [Bre95] following the model of the ribozyme. A ribozyme is RNA (RiboNucleic Acid) that behaves like an enzyme and that is present in the alive organisms. It is believed that it played an important role in the beginning and development of the life in this planet.

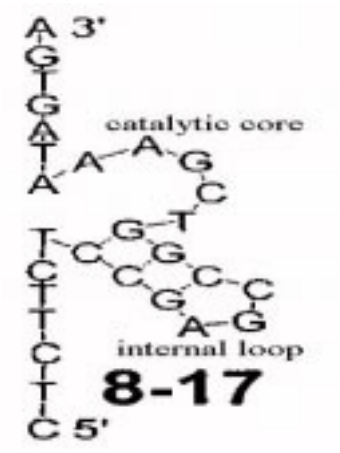


Figure 6: deoxyribozyme 8-17

Different kinds of deoxyribozyme were created, for example self-cleaving DNA, DNA that uses amino acids as cofactors, catalytic DNA of the reactions for self-cloning, DNA that catalyzes its own destruction or the destruction of other sequences of DNA … new and powerful deoxyribozymes are being investigated. These catalytic DNA can be easily produced in vitro in a laboratory and can be designed modularly like a mix of controlling elements and catalytic regions.

The deoxyribozymes used as logic gates in this experiment are called E6 [Bre95] and 8-17 [Zhe00, San97] and they were chosen because of the wide knowledge about them in biology. The E6 deoxyribozyme has a catalytic core and an internal loop (**Fig. 5**). The internal loop can be substituted by a desired sequence; this property will be used to design NOT gates.

On the other hand the 8-17 deoxyribozyme is formed by a catalytic core and a fixed internal loop (**Fig. 6**) that is not possible to change. Stem-loops can be placed in the arms of this oligonucleotides. These loops are activated with a certain sequence of nucleotides. Each of these loops remains closed when the complementary sequence of nucleotides to the one in the loop is not mixed with the deoxyribozyme in the chemical solution; this is the so-called inactive form. When the complementary sequence exists in the solution the loop opens and the oligonucleotides anneal; this is the so-called active form.

The deoxyribozymes used to build up the gates are supposed to be catalyst but actually they are not exactly that. A catalyst must remain invariable after the reaction. But these catalytic oligonucleotides do not change if the input is "0" (no input oligonucleotide in the solution) but if it is "1" they become in active form; in other words, the input oligonucleotide is annealed to the deoxyribozyme. The reset of the gate and the removal of the input is made by washing, adding to the solution the complementary sequence of nucleotides of the inputs. Therefore, if we consider the deoxyribozyme process and the washing, they are full catalyst.

In the concrete application for which these gates have been thought, it is not necessary to reset. They are going to be one part of a bigger system for analyzing molecules in order to know if there is some molecular disease. The system input will be an oligonucleotide capable of re-cognizing these diseases and the output will be "yes, there is" (cleavage) or "no, there isn't" (no cleavage). But the reset is possible and the gates can be used again.

One of the most important outcomes of the success of this experiment is the possibility of avoiding enzymes, substituting normal DNA for catalytic oligonucleotides. The enzymes are limited in diversity but deoxyribozymes have a bigger range of application.

2.5 Cleavage

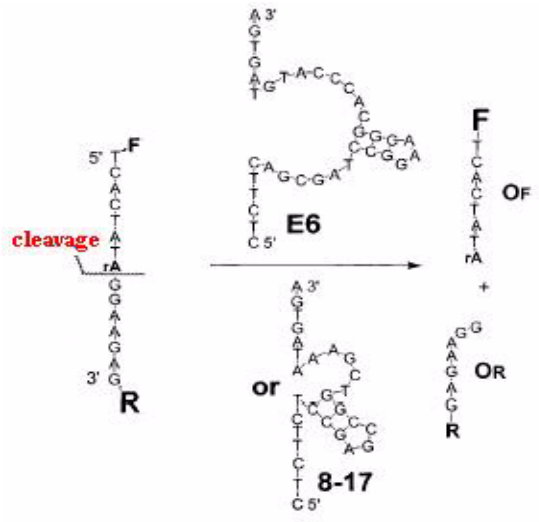


Figure 7: Schematic of the cleavage of E6 and 8-17

The cleavage (**Fig. 7**) is the splitting of a molecule into simpler molecules by breaking a chemical bond. In the logic gates case, the cleavage is made to a substrate (ended by a fluorescein donor in the 5'-end (F) and a tetramethylrhodamine acceptor (R) in the 3'- end) by the deoxyribozymes at its single ribonucleotide (rA). This substrate can anneal with the single stranded arms of the deoxyribozyme. When they anneal, the substrate splits into two oligonucleotides. One of them has a fluorescein donor (O_F) and the other has a tetramethylrhodamine acceptor (O_R). The reaction is initiated by the addition of Mg^{2+} (magnesium).

3 Deoxyribozyme-Based Logic Gates

To build a computational system, first it is necessary to develop the simple parts of this system, as the logic gates with which any function can be implemented. These model of logic gates (**Fig. 8**) were design to take part in a device to detect molecular diseases [Sto01]. But it can be used to perform other functions, for example, a half adder. Until now, making linear operations with DNA was a difficult task. It was easier to solve the Hamiltonian path than a simple sum (1+1). But with deoxyribozyme, a half adder can be developed in a simple and effective way. Why catalytic DNA is so good to perform this functions?

The catalytic oligonucleotides can be configured in such a way that they exhibit a binary behaviour. For example, in our concrete case when there is cleavage of the substrate there is a “1“ in the output because the oligonucleotide defined as output is one of the parts of the divided substrate. Then, when it is present in the final solution the output is interpreted as a “1“. When there is no cleavage, the output oligonucleotide is not produced and there is a “0“ in the output. The catalytic DNA only reacts when there is a concrete oligonucleotide present, if not it remains in inactive form. These two characteristics of deoxyribozyme are the reason why logic gates can be developed with it. The production of basic gates like sensors, NOT, AND and XOR will be explained in detail in this paper and configurations of OR, NAND and a half adder will be suggested.

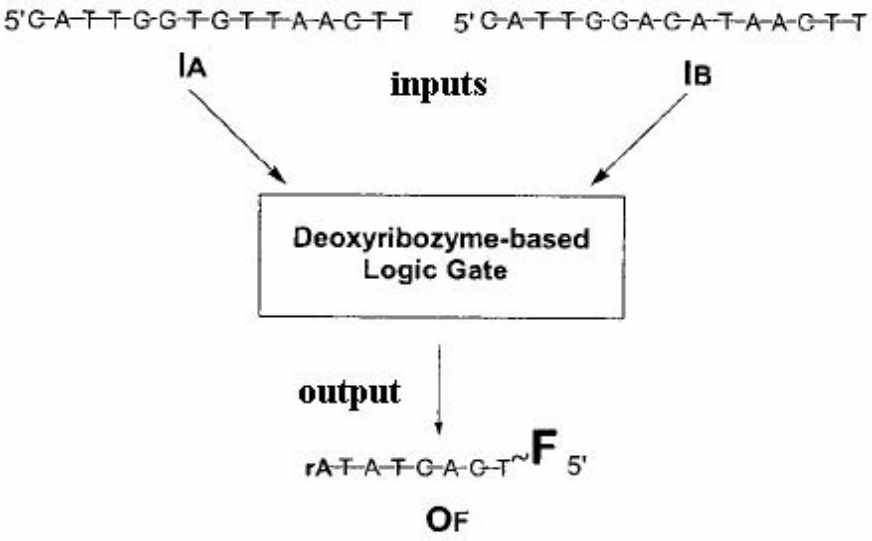


Figure 8: schematic of a logic deoxyribozyme-based logic gate with the input and output oligonucleotides.

3.1 Sensor gate

A sensor gate transfers the detected input to the output. Hence, the true table of this device is as follows:

INPUT	OUTPUT
0	0
1	1

To implement this device the deoxyribozyme E6 is chosen (**Fig. 9**). A stem-loop is placed in the 5'-end. This stem-loop is configured with the complementary sequence of the input oligonucleotide. A solution containing this E6 configuration and the substrate, is prepared to receive the input.

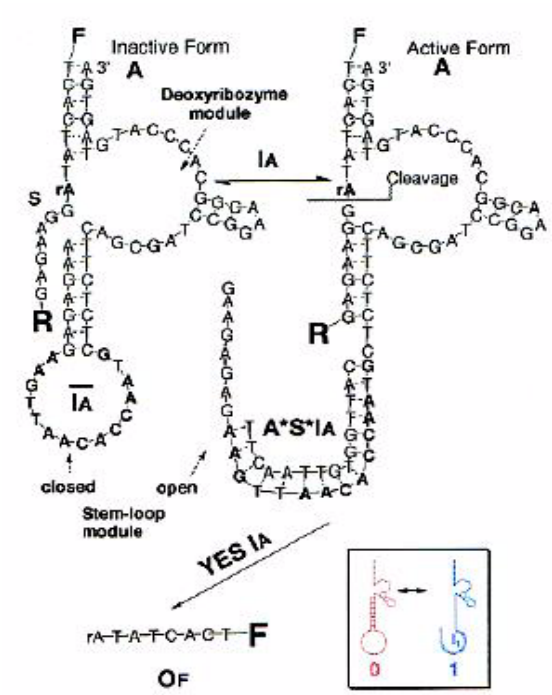


Figure 9: behaviour of a sensor gate

If there is no input, the gate remains inactive because the closed loop overlaps with one of the arms of the catalytic oligonucleotide. Both arms together form the complementary sequence of the input. It means that if one of them is overlapped, the substrate can't anneal with the E6. In this case, there is no cleavage and as a consequence there is no output oligonucleotide. There is a "0" in the output.

If the desired input (the one complementary of the nucleotide sequence of the stem-loop) is added to the solution, the loop is opened and hybridizes with the input. Then, the arms of the E6 are single stranded and anneal with its complementary which is the substrate. The cleavage is produced. The substrate is split into two oligonucleotides. The emissions of one of them, that with the fluorescenin donor, are detected in the fluorescence spectra. There is a "1" in the output.

3.2 Proposal of an OR gate

An OR is a gate with two inputs and one output. It sets the output to "1" when there is a binary "1" in at least one of its inputs. Its true table is as follows:

INPUT A	INPUT B	OUTPUT
0	0	0
0	1	1
1	0	1
1	1	1

An OR gate is constructed with two kinds of sensor gates. The input of each of these groups has a different sequence of nucleotides. The two kinds of sensor gates are put together with a substrate in a solution.

When at least one group of the gates is activated by its respective input, the cleavage of the substrate happens. Therefore, the oligonucleotide output with the fluorescenin donor is present in the solution. This means a “1“ in the output.

Only, when both inputs are missing, the cleavage doesn’t occur and the expected output oligonucleotide is not present. The output is “0“.

3.3 NOT gate

A NOT gate puts in the output the opposite bit to the input. The true table is as follows:

INPUT	OUTPUT
0	1
1	0

The implementation with DNA is made with E6 but changing the structure with regard to the one used as sensor gate (**Fig. 10**). The nonreacting loop of E6 is substituted by a stem-loop with a sequence complementary to the input.

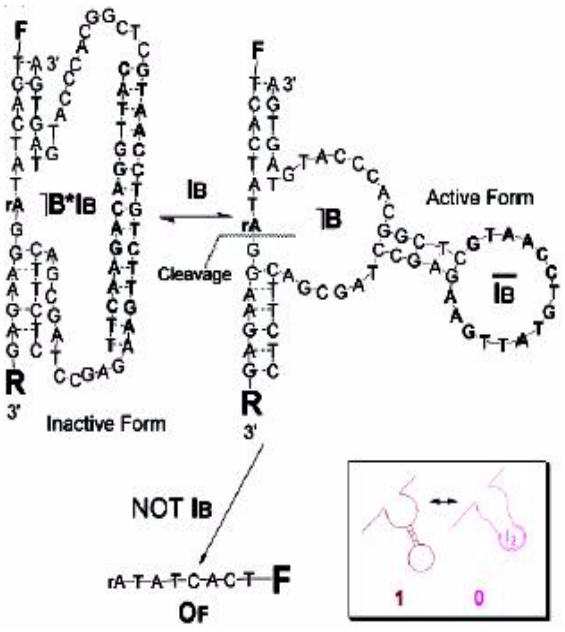


Figure 10: behaviour of a NOT gate

The gate and the substrate are put together in a solution. If the input is added to the solution (a one in the input), the hybridization between the input and the stem-loop with complementary sequence produces the changing of the deoxyribozyme into its inactive form. As a result, there is no cleavage and therefore, neither is output oligonucleotide. This means a “0“ in the output.

But if no input is added, the E6 remains in its active form and cleaves the substrate, producing the output oligonucleotide (output is “1“).

3.4 Proposal of a NAND gate

A NAND is a two inputs gate that sets the output to “0“ when both inputs are “1“. In the rest of the cases the output is “0“. Then, the true table is as follows:

INPUT A	INPUT B	OUTPUT
0	0	1
0	1	1
1	0	1
1	1	0

A NAND gate is a solution containing two groups of NOT gates with different structure. There is a different sequence of nucleotides in the input of one group from the one of the other.

When both inputs are added to the solution both gates are inhibited and no output is produced (“0“).

If one of the inputs is missed in the solution, one of the gates produces output oligonucleotide by splitting the substrate and if both are missed the two gates produce output oligonucleotide by splitting the substrate. In this case, the output is “1“.

3.5 AND gate

An AND gate is a two input gate that only sets the output to “1“ when both inputs are “1“. The true table of this device is:

INPUT A	INPUT B	OUTPUT
0	0	0
0	1	0
1	0	0
1	1	1

The 8-17 deoxyribozyme is used to build an AND gate (**Fig. 11**). Two stem-loops, one in the end of each arm of the oligonucleotide, are joined to the 8-17 structure. The sequence of nucleotides of these loops is different. Thus, each one reacts with a different input (the one that has its complementary sequence).

If both inputs are added to the solution with the gate and the substrate, they hybridize with the stem-loops. The stem-loops are opened and the substrate anneal with its complementary oligonucleotide in the deoxyribozyme. The cleavage of the substrate produces the output oligonucleotide. The output is set to “1“.

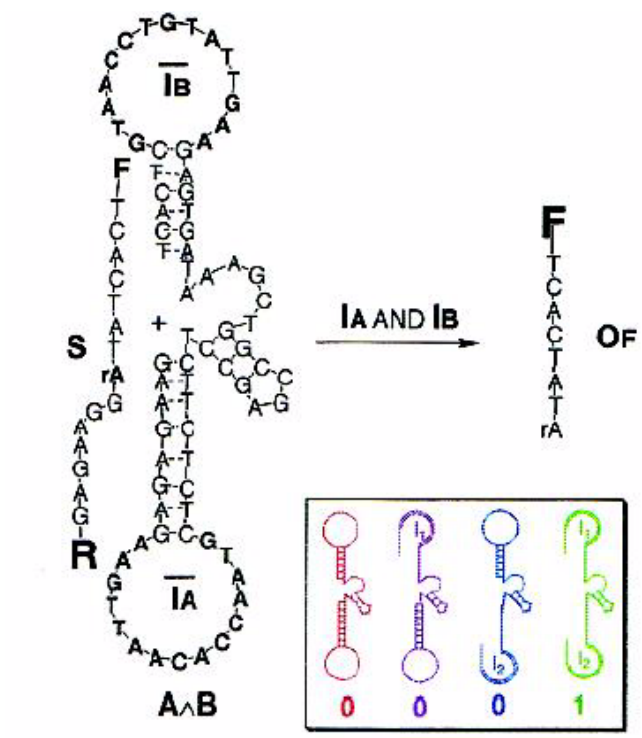


Figure 11: behaviour of an AND gate

If only one of the inputs is added, its complentary stem-loop is opened but the other doesn't. The one that remains closed overlaps one of the parts of the catalytic oligonucleotide that must anneal with the substrate to cleave it. This way, the cleavage does not occur and there is no output oligonucleotide: "0" in the output.

If none of the inputs are put in the solution, both stem-loops of the gate are closed. They overlap the part of the deoxyribozyme that has to anneal with the substrate to cleave it. No cleavage occurs and therefore the output oligonucleotide does not exist. There is a "0" in the output.

3.6 XOR gate

A XOR gate is a two input gate. It sets to "1" the output when one and only one of the inputs is "1". Then, the true table is as follows:

INPUT A	INPUT B	OUTPUT
0	0	0
0	1	1
1	0	1
1	1	0

The XOR gate is the most difficult to implement because the gate must be active when one of the inputs is present, it does not matter which of them. But when both of them are present, the gate must be inactive. Then, sometimes must be active with a certain input and other times must be inactive with the same input when it is attached to the other input.

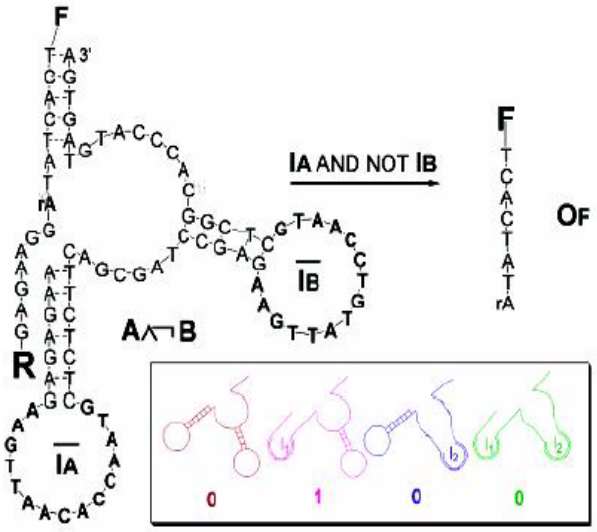


Figure 12: One of the groups of the XOR gate

The XOR gate is composed by two groups of gates. There are two input oligonucleotides. In order to make a clear explanation, one will be referred to as "the first" and the other as "the second". One of the groups is active when only the first input is in the solution but not the second. The other group must be activated by the presence of only the second group but not the first. Therefore, when both inputs are in the solution none of the groups of gates is active.

Each gate of one of the two groups is a mix between a sensor and a NOT gate (**Fig. 12**).

The group which is active with only the first input is formed by E6 deoxyribozymes ended by a stem-loop. This stem-loop has a sequence of nucleotides complementary to the sequence of the first input. It behaves like a sensor for the first input. These gates have another stem-loop in the core of the deoxyribozyme. It works with the second input like the loop in the NOT gate.

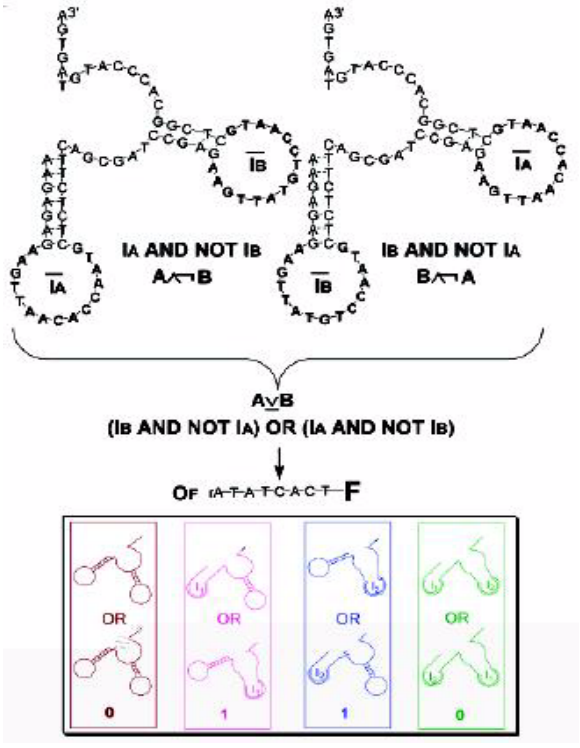


Figure 13: behaviour of the XOR gate

The translation to logic language will be $A \wedge \neg B$ (A is the first input and B is the second). This happens analogously for the other group of gates, that in logic language will be $B \wedge \neg A$.

Then, if only one input is present in the solution, one group of gates is inhibited and the other is in active form. Thus, there is cleavage of the substrate and output oligonucleotide in the final solution.

But if both inputs are present the two groups are inactive. No cleavage and hence no presence of the output oligonucleotide. Similar events happen when there are no inputs.

This behaviour can be translated like an OR (**Fig.13**) of the functions carried out by the two groups $(A \wedge \neg B) \vee (B \wedge \neg A)$.

3.7 Proposal of a half adder

A half adder gives an output consisting of two bits. One of them is the binary addition of the two inputs, in other words, the result of a XOR operation between the two bits. The other bit is the carry which can be implemented as the AND operation over the two inputs [McC86].

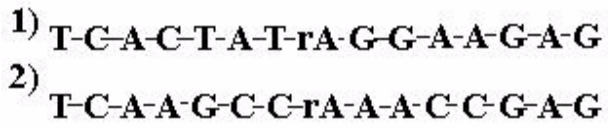


Figure 14: Substrates of the half adder

The AND and XOR gates are designed to accept the same input oligonucleotides (**Fig. 3**). But they act over different substrates (**Fig. 14**).

The substrate 1) (**Fig. 14**) can be cleaved by the XOR gate (**Fig. 13**) that makes the sum module 2 of the inputs

The substrate 2) (**Fig.14**) can be cleaved by the AND gate (**Fig. 15**) that obtains the carry.

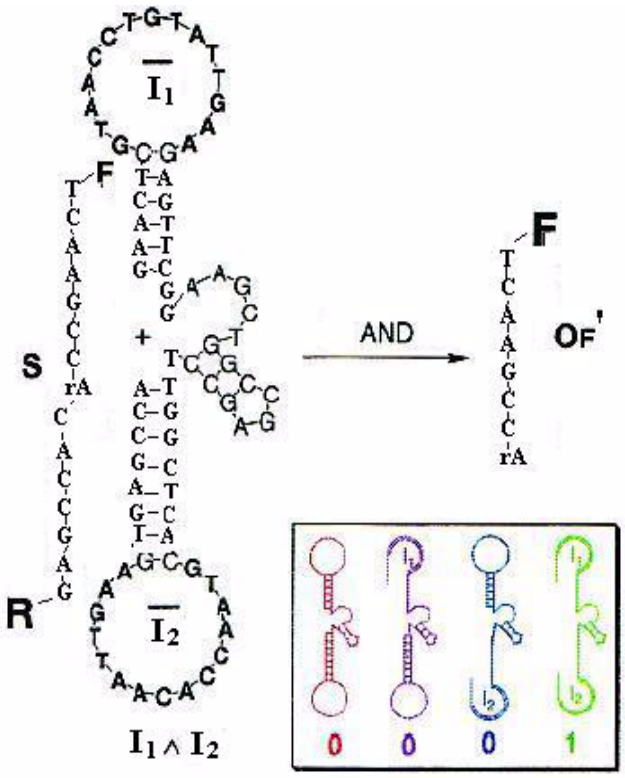


Figure 15: AND to obtain the carry

Both gates (XOR and AND) are mixed wit the substrates in a solution.

To sum 1+1, both input oligonucleotides are added to the solution. The XOR gates become in inactive form and AND gates become in active form (they cleave the pertinent substrate, as has been explained). In the final solution only O_F' (**Fig. 15**) is present. The binary result is “10” (2 in decimal).

To sum 1+0 or 0+1, only one input oligonucleotide is added and then only the XOR is active and cleaves its substrate. This way, the O_F (**Fig. 12**) is present in the final solution. The result in binary is “01” (1 in decimal).

To sum 0+0, no input nucleotides are added. No gate is active, there is no cleavage and no output oligonucleotides. Therefore, the resullt is “00“.

4 Fluorescence spectrum

All the processes related to the behaviour of the deoxyribozyme-based logic gates have been explained except for the detection of the output oligonucleotide.

After the logic operation, the output is in the solution, waiting for being analyzed. There are two possible outputs. When the cleavage happens, there is output oligonucleotide. This is interpreted as “1“. But if there is no cleavage, no output oligonucleotide is generated. There is a “0“ in the output.

Our method to detect the output is the fluorescence spectrum [Vam93]. In other words, it consists of analyzing the emissions of the final solution in the visible spectra when a beam of electrons of $\lambda = 480nm$ is sended.

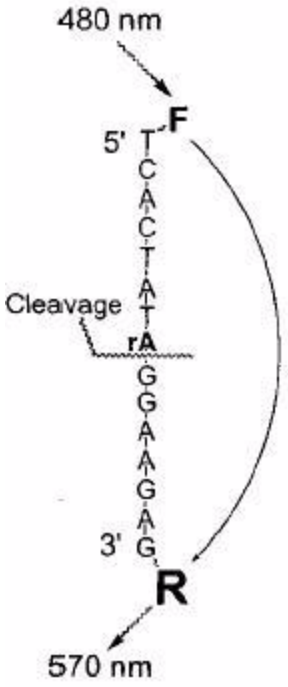


Figure 16: Substrate

The substrate (**Fig. 16**) is an oligonucleotide ended with a fluorescein donor (F) at the 5´-end and with a tetramethylrhodamine acceptor at the 3´-end. This configuration was chosen because when this substrate is cleaved at the single ribonucleotide (rA) the fluorescence of the substance is incremented.

If cleavage has not happened, when a beam of electrons of $\lambda = 480nm$ is sended (fluorescence sprectrum method), the acceptor (R) absorves much part of the emision of the donor. As it is possible to see in **Fig. 17** (brown line), there is not a peak of emision in $\lambda = 520nm$. The output is “0“.

But if cleavage has taken place (**Fig. 18**) when the beam of electrons of $\lambda = 480nm$ is sended, the donor emits at $\lambda = 520nm$.On scaning from $\lambda = 500nm$ to $\lambda = 600nm$, a peak at $\lambda = 520nm$ is detected (**Fig. 17**, blue line). The output is “1“.

This method is only valid to detect one output (one bit), when there are more output bits (for example, half adder) this method is not valid (but there are others).

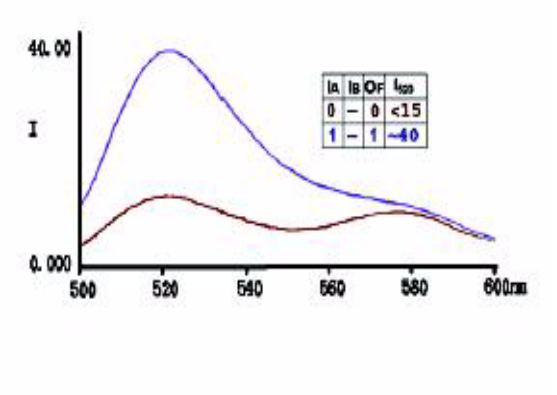


Figure 17: Fluorescence spectra of sensor gate

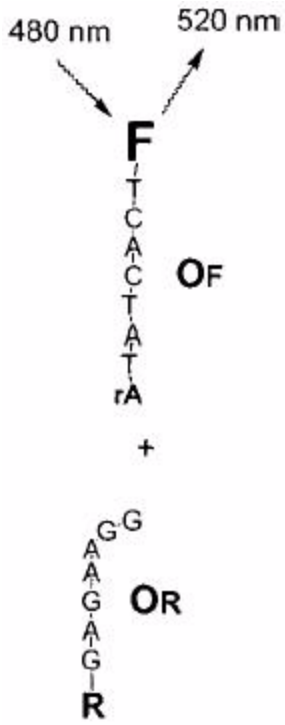


Figure 18: cleaved substrate

5 Advantages and disadvantages

Like a DNA model, this method has all the advantages of molecular computing versus a silicon one: the parallelism when executing processes [Ogi99], the low power consumption and the high speed of the molecular events. And of course, some disadvantages: necessity of human intervention in the computations, little development, the computation is fast but the access to the results and the data is slow.

But, there are new points in this model that show new possibilities. Until now, the linear calculation was very complicated to implement with DNA models (for example: 1+1). However, with this model a proposal of a very simple half adder was given.

Until now, there were no complete set of logic gates with the same model. Deoxyribozyme lets implement all the logic gates and therefore it is possible to perform all the functions that can be expressed like a combination of these basic logic functions.

The inputs and outputs have the same nature, they are oligonucleotides. Hence, the outputs of a gate can be used as input of other gates to construct a system. This is the aim of this research, interconnecting logic gates to perform a computation capable of discovering diseases in a molecular level. This objective is not realizable with silicon technology, it will be a specific field for molecular computing.

Comparing deoxyribozyme with the usual methods to perform DNA computing, deoxyribozyme avoids the use of enzymes. The enzymes are limitated and act over specific sequences of nucleotides. The deoxyribozyme is a catalyst that can work with almost any nucleic acid sequences of sufficient length as input, this is an increase in the degrees of freedom.

On the other hand, the discovery of the deoxyribozyme is relatively recent. New discoveries and researches are made, and the knowledge about the possibilities of the deoxyribozyme as material to perform computations is not so well-known like the events performed by enzymes. Therefore, it is necessary to wait in order to assure the future of this techonology but it seems to be encouraging.

6 Conclusion and perspectives

After the experiment of Adleman the interest in DNA computing began to increase. A lot of scientifics have taken part in the researches about the computacional capabilities of DNA [Roo99]. The great number of studies developed in the last years have opened a discussion about the real applications of molecular computing.

In the beginning of this matter, scientifics thought that the field of application of DNA computing will be restricted to very specific fields related to problems that are impossible to solve with silicon techonology. But just now, the molecular technology is looking for its own applications in fields that bear no relation to classical techonology.

For example, the objetive of the deoxyribozyme-based logic gates is to take part in a bigger system capable to detect molecular diseases and defects. Classical computing techonologies could not be applied to this project.

Furthermore, looking at the evolution of the DNA computing, we realize that until now the processes were always based on well-known biologic events. Normally, all the reactions were associated to an enzyme because normal DNA is not able to react alone but it needs the help of a catalyst. This is other of the reasons why deoxyribozyme is a groundbreaking discovery. It permits DNA reactions without enzymes. This fact gives a new degree of freedom in the design of molecular computational systems.

The new model of computing based on catalystic oligonucleotides has stablished new ways to deal with DNA computing and has validated the theoretical possibilities with a experimental implementation. It is the first time that a complete set of logic gates is developed by means of molecular devices.

The future of the deoxyribozyme model is guaranteed, and possibly in a couple of years there will be more researches involved with it. Just now, there are more devices made by catalytic DNA. For example, there exist switches.

Only time can point out the real possibilities of this sequences of nucleotides with such special characteristics.

7 References

[Adl94] Leonard M. Adleman *"Molecular computation of solutions to combinatorial problems"*, Science 266, 1021-1024, 1994

[Lew02] David I. Lewin *"DNA computing"*, IEEE, 2002

[Sto01] Milan N. Stojanovic, Tiffany Elizabeth Mitchell, and Darko Stefanovic *"Deoxyribozyme-Based Logic Gates"*, American Chemical Society, 2001

[Bre 95] R.R. Breaker, G. F. Joyce, Chemical Biology 2, 655-660, 1995

[Zhe00] W. Zheng, J. Li, A. H. Kwon, Y. Lu, Nucleic Acid Res. 28, 481-488, 2000

[San97] S.W. Santoro, G. F. Joyce, Proc. Natl. Acad. Sci. U.S.A. 94, 4262-4266, 1997

[Vam93] G. Vamosi, c. Gohlke, A. I. H. Murchie, D. M. J. Lilley, and R.M. Clegg *"Proving the conformation of DNA structures - 4-way junctions and bulges - with fluorescence"*, 11th International Biophysics Congress, 1993

[McC86] E. J. McCluskey *"Logic Design Principles"*, Prentice Hall: Englewood Cliffs N. J. 1993

[Roo97] D. Rooss *"Recent Developments in DNA-Computing"*, IEEE, 1997

[Ogi99] M. Ogihara, A. Ray *"Executing parallel logical operations with DNA"*, IEEE, 1999

[Wat53] J. D. Watson & F. H. C. Crick *"A structure for DNA"*, Nature, 1953