

# 可满足问题的分子信标计算模型

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**摘 要** 分子信标(Molecular Beacon)是一种发夹状的荧光探针,它可以特异地和那些与分子信标的环(Loop)互补的核酸靶序列杂交,具有单个碱基错配的检测能力.肽核酸(Peptide Nucleic Acid)是人工合成的核酸(DNA)的类似物.PNA 骨架为酰胺键,与 DNA 补链杂交更稳定,可以阻止聚合酶延伸反应.文中将可满足问题的约束变量编码于分子信标的环部识别区,通过分子信标与使得给定范式为真的变量的 PNA 补链杂交,再利用 PNA 链可以阻止聚合酶延伸反应的性质,用限制性内切酶 EcoRI 降解对应于非解的分子信标,最后通过加热表面使分子信标构形发生变化,产生荧光读解.提出的可满足问题的分子信标计算模型具有可靠性高、无需观察和记录计算的中间结果、读解简单等优点.

**关键词** DNA 计算;可满足问题;分子信标;肽核酸;荧光

**中图法分类号** TP301

## Molecular Beacon Based DNA Computing Model for General Satisfiability Problem

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**Abstract** Molecular Beacon is a hairpin-shaped fluorescent probe, which can hybridize with great specificity target sequence that is complement to its loop sequence. The specificity of Molecular Beacon is as high as single base mismatch detection. Peptide Nucleic Acid (PNA) is an artificial synthesized analogue of nature occurring DNA, in which the DNA sugar-phosphate backbone has been replaced by a pseudo-peptide. Thus the hybridization of PNA to complement DNA strand is more specific and stable than that of DNA to DNA. PNA can stop polymerase extension reaction as well. In this paper, Molecular Beacons were employed to encode variables in satisfiability problem and complement PNA strands were added and allowed to hybridize with Molecular Beacon. The hybridized PNA strands on Molecular Beacon stopped polymerase extension reaction, causing Molecular Beacon corresponding to non-solution were digested by means of restriction endonuclease EcoRI. The remaining Molecular Beacons encoding solutions were read out via heating. The appealing characteristics of proposed method in this paper are: Reliable, no observation and record of midst solution, easy solution detection.

**Keywords** DNA computing; satisfiability problem; Molecular Beacon; peptide nucleic acid; fluorescence

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## 1 Introduction

It bases on two principles to use DNA molecules to solve computing problems: The Watson-Crick base pairs principle of DNA molecule and the huge parallelism of biochemical chain reaction. The former can be converted to a computer's common language<sup>[1]</sup>, and the latter uses exhaust algorithm to solve difficult and incalculable problem, and makes it possible. In 1994, Adleman<sup>[2]</sup> used the DNA sequence as information carrier, made use of Biological Technology to solve an NP-complete problems—Hamilton path problem issues, and pointed out that DNA Computing has features of massive information storage and high computing parallelism. Therefore, it allowed DNA Computer to solve NP-complete problems in the linear time (The time of Turing solving such problems increases exponentially). Following the work of Adleman, many scholars have put forth different DNA computing models, and successively solved the Maximum Clique Problem, Knight Problem, Maximum Independent Set and SAT Problem (Satisfiability Problem), and so on. Liu et al.<sup>[3]</sup> put forward the SAT surface computing model, and reveal the possibility of DNA computing, from the demonstration of theoretical model to making use of the research of computing chip. Wu<sup>[4]</sup> made further improvements for this way. Liman Wang et al.<sup>[5]</sup> gave Multiple Word DNA Computing model on the surface.

So far, there have been many issues needed to be resolved in the current model of DNA computing, such as biochemical reactions error-prone, especially DNA hybridizing wrongly, the degradation efficiency of DNA is not high enough, so that it hardly can achieve the required accuracy of calculation; A number of nucleotide molecules required by algorithms increase exponentially, hampering the calculation of the scale of DNA; The biological steps required by DNA computing make the scale of the problem linearly increase, but every step waste time and energy, etc. These problems are constraining DNA computing to the bottleneck of the practical application.

DNA computing based on Molecular Beacon model chip was pointed out by Zhixiang Yin<sup>[6]</sup> et al. The essence is that the bound variable of the SAT problem, which encode in the recognition sequence of Molecular Beacon, is called Molecular Beacon's loop, and then judge clause's satisfiability through its hybridization of target sequence.

The model first develops the use of Molecular Beacons structure to explore the solutions to Combinatorial Optimization Problem, and it is of very important theoretical significance. Compared with conventional biotechnology, Molecular Beacons chip's largest features is its single base mismatch or missing detection, that is, a single base mismatch or missing can not induce fluorescence of Molecular Beacons. This is tremendous advantage that the linear DNA molecule doesn't have. In addition, Molecular Beacons bring their own fluorescence, and needn't fluorescence label DNA molecule, which can easily detect the final results. At current, Molecular Beacons chip technology has been applied to DNA analysis, DNA chips and DNA sensors, gene mutations and polymorphisms of research areas, which demonstrate strong vitality and good prospects. However, the model should meet the requirements of the SAT problem into the standard paradigm, and the need for computing the bond energy after Molecular Beacons hybridization, to ensure that the hybridization will be able to open the Molecular Beacons, induce fluorescence. In addition, in the calculation process, it is necessary to observe, record intermediate results time after time. In this paper, we use Peptide Nucleic Acid (PNA) molecule and Molecular Beacon to a high degree of specificity of hybridization, then use the character that PNA chain can prevent the polymerase extension reaction, and use restriction enzyme to degrade corresponding Molecular Beacons of nonsolution, finally, the surface heating makes Molecular Beacon's configuration change, then produce fluorescence for solution detection. The proposed model in this paper has many advantages, such as high reliability, not needing to observe the intermediate result in the calculation, and easy solution detection, and so on.

## 2 Molecular Beacon and PNA

Molecular Beacon was put forward by Tyagi et al.<sup>[7]</sup> The Molecular Beacon is composed by a fluorescent stem (Stem) and an annular oligonucleotide sequence (Loop) (Fig. 1). Oligonucleotide sequence of the loop is the identification of Molecular Beacon (the target gene-sequence), and it can spontaneously differentially hybridize with target gene. Stem is composed by complementary base in 5~7 bps. Molecular Beacon in the 5' and 3' can be modified to connect to the gene with fluorescence (Reporter, such as Fluorescent Green ABI) and quenching group (Quencher, such as DABCYL).

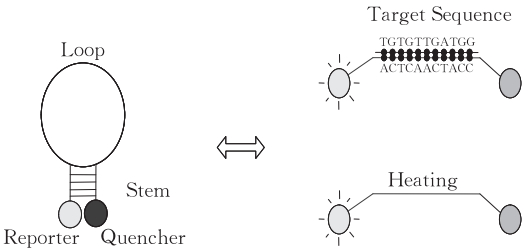


Fig. 1 Structure and theory of Molecular Beacon

In the closed-loop structure of Molecular Beacon (Stem-Loop), the fluorescent molecules and quenching molecules of the stem are very contiguous (7~10 nm), it makes fluorescent molecules be directly absorbed by quenching molecules and distributed in the form of heat, so the fluorescent signal can't be detected. There are two ways that Molecular Beacon's closed-loop structure converts to open-loop structure: When there is target sequence in the liquid, Molecular Beacon can differentially combine with target sequence, then form into double-stranded miscellaneous heterozygote structure more stable than the stem-loop (Fig. 1 upper right). At this point, quenching groups and fluorescent groups separate and then the fluorescence can be detected; the other method is directly heating. The complementary base of the stem is unlinked after the degeneration, also, quenching groups and fluorescent groups separate and then the fluorescence can be detected (Fig.1 lower right). The method in this paper was used to read the final results.

Peptide nucleic acid was put forward by Nielson et al., in 1991, and it was synthetic nucleic acid analogues<sup>[8]</sup>. The difference between PNA and DNA is deoxyribose phosphate skeleton of DNA was replaced by the peptide skeleton, that is, the repeated N-(2-acetaldehyde) glycine units, and four bases were connected through the Asia-carbon mesitoyl.

PNA not only retains the DNA characteristics of the hybridization, but also because its skeleton is electric neutrality, the specificity and stability have been markedly improved, when its complementary DNA hybridized with RNA. In general, solution temperature of the 15 mer DNA/DNA double-strand is about 70℃, while solution temperature of the corresponding PNA/DNA double-stranded is only 55℃. PNA and the combination of complementary DNA also show high specificity, 15 mer PNA/DNA's mismatch is more volatile than the DNA/DNA. A single base mismatch of 15 mer PNA/DNA may make solution temperature drop

8℃ to 20℃ (the average is 15℃), the corresponding DNA/DNA double strands in a single base mismatch may make solution temperature drop 4℃ to 16℃ (the average of 11℃). In addition, because Peptide Nucleic Acid is man-made, without the degradation of Nucleic Acid Enzymatic, and polymerase's effect, you can block polymerase extension reaction. According to this feature, we can delete Molecular Beacons which doesn't meet the paradigm from the surface, after the calculation of this paradigm's items, the remaining Molecular Beacons is the result met to the paradigm.

3 Satisfiability Problem

Satisfiability Problem (SAT Problem): Suppose  $A=\{x_1,x_2,\cdots,x_n\}$  is Boolean variables' collection,

$$C_i=b_1 \vee b_2 \vee \cdots \vee b_k (i=1,2,\cdots,m)$$

is disjunctive normal form composed by the Boolean disjunction ( $\vee$ ), in it,  $b_r=x_j$  or  $b_r=\bar{x}_j (r=1,2,\cdots,k; j=1,2,\cdots,n)$ ;  $f=C_1 \wedge C_2 \wedge \cdots \wedge C_m$  is conjunctive normal form composed by the Boolean disjunction, in it,  $C_i (i=1,2,\cdots,m)$  is disjunctive normal form. Suppose  $\alpha$  is assignment for a group of variables' value  $x_1,x_2,\cdots,x_n$ , where each variable value is 0 or 1, if  $\exists \alpha$  makes  $f(\alpha)=1$ , the problem can be called being satisfied, otherwise, called not being satisfied, and this problem is called as Satisfiability Problem (SAT Problem). When each item in the disjunctive normal form has not more than  $k$  variables, we call it  $k$ -Satisfiability Problem ( $k$ -SAT Problem). Special example is when  $k=3$ , that is, each item in the disjunctive normal form has not more than 3 variables, we call it 3-Satisfiability Problem (3-SAT Problem). It has been proved that when  $k=3$ , this Satisfiability Problem is NP-Complete problem.

We use the following method to solve the Satisfiability Problem (SAT Problem):

Step 1. generate all possible results of the problem generated.

Step 2. use every possible result, if a possible result may make each item of the conjunctive normal form false, delete this result.

Step 3. generate the remaining results.

Step 4. Repeat for two and three steps, we can delete all non-solution, thus we have estimated the SAT Problem.

4 Model System of SAT Problem

For SAT Problem which has  $n$  variables called  $x_1, x_2, \cdots, x_n$  and  $m$  conjunctive normal forms,

first synthesize  $2n$  kinds of short oligonucleotides fragments, and put them into two groups, with  $n$  kinds of oligonucleotides in the first group being separately encoded as variables  $x_1, x_2, \dots, x_n$ , and  $n$  kinds of oligonucleotides in the second group as variables  $x'_1, x'_2, \dots, x'_n$  (for  $x_i$ , the corresponding oligonucleotide is  $x_i=1$ , for  $x'_i$ , the corresponding oligonucleotide is  $x_i=0$ ). Use the combination of  $2n$  kinds of oligonucleotides in these two groups as Molecular Beacon identification zone (the total being  $2^n$ ), each combination including  $n$  oligonucleotides corresponded to by variables. Molecular Beacon's stem is public sequence with 6 bases,  $\left\{ \begin{matrix} 5'-GTATAT-3' \\ 3'-CATATA-5' \end{matrix} \right\}$ , choose fluorescent green (Fluorescent Green ABI) as Molecular Beacon's fluorescent group (Reporter), DABCYL is Molecular Beacon's quenching group (Quencher). After Molecular Beacon has been finished, use 5'-Thiol-Modifier's carbon atoms as the connection arm ( $5'-HS-C_6-T_{10}-GAATTC-, \dots-3'$ ), make all Molecular Beacon fix in surface of carriers, of which  $T_{10}$  is 10 bases' Spacer sequence, sequence  $\{5'-GAATTC-3'\}$  is EcoRI's recognition site. Molecular Beacon will be on the order of labeling right to left, they correspond to variable combination of Molecular Beacon's annular identification zone. Finally, combine complementary strand of  $2n$  kinds of oligonucleotide fragments in the first and second group, they are respectively expressed as  $\bar{x}_1, \bar{x}_2, \dots, \bar{x}_n$  and  $\bar{x}'_1, \bar{x}'_2, \dots, \bar{x}'_n$ .

Step 2 of corresponding algorithm: One item of given conjunctive normal form, hybridizes with PNA complementary strand ( $\bar{x}_i$  or  $\bar{x}'_i$ ) which corresponds to variable made this item true. It enables its identification zone of Molecular Beacon to have PNA complementary strand ( $\bar{x}_i$  or  $\bar{x}'_i$ ), and enables identification zone of Molecular Beacon that makes item false not to have PNA complementary strand ( $\bar{x}_i$  or  $\bar{x}'_i$ ). Heating untied double-strand of stem, it makes Molecular Beacon linear. Add the buffer solution, polymerase and DNA primer in the surface again, and the primer is complementary strand of Molecular Beacon's stem in the  $3'(\{5'-ATATAC-3'\})$ , then react polymerase extension reaction. Corresponding to Molecular Beacon met

this normal form, its identification zone have the half-bred PNA chain, and PNA skeleton of the peptide prevents the reaction, so, EcoRI's recognition site is still single chain after polymerase extension reaction, and it can't be identified by EcoRI and degraded. Corresponding to Molecular Beacon that doesn't meet met this normal form, after this reaction, because of its loop not having PNA chain, the primer ( $\{5'-ATATAC-3'\}$ ) is extended to EcoRI's recognition site ( $\{5'-GAATTC-3'\}$ ), becomes double-strand with polymerase's effect, and is identified by EcoRI and degraded. Add the buffer solution and EcoRI, then clean and remove Molecular Beacon which makes the item false.

Step 3 of corresponding algorithm: Heating the chain, clean and remove the hybridized complement PNA strands ( $\bar{x}_i$  or  $\bar{x}'_i$ ) of the variables. Then, anneal makes Molecular Beacon's conformation closed-loop-like again.

Step 4 of corresponding algorithm: Repeat two and three steps. All Molecular Beacons corresponding to non-solutions will be removed in the surface. When all items have been considered, if there are Molecular Beacons in the surface, the given problem can be satisfied, otherwise, it can't be.

Step 5: Heating the surface directly, the surface double strands of the Molecular Beacons' stem degenerate, leading to the fluorescence group and quenching group's separation, thus it induces fluorescence. Use LSCM for solution detection.

Let's discuss a sort of SAT Problem about easy conjunctive normal form:

$$(x \vee \bar{y}) \wedge (\bar{x} \vee z) \wedge (\bar{y} \vee \bar{z}).$$

This problem can be satisfied, its result is  $\{(1, 0, 1), (0, 0, 1), (0, 0, 0)\}$ .

First, we construct six kinds of short oligonucleotides, and they respectively stand for  $x, y, z$  and  $x', y', z'$ . This synthesis of the six kinds of oligonucleotides' complementary strands respectively stand for  $\bar{x}, \bar{y}, \bar{z}$  and  $\bar{x}', \bar{y}', \bar{z}'$ . Use these kinds oligonucleotides ( $\bar{x}, \bar{y}, \bar{z}$  and  $\bar{x}', \bar{y}', \bar{z}'$ ) to combine to eight Molecular Beacon's identification zones, according to the clockwise, the array is  $x$  or  $x', y$  or  $y', z$  or  $z'$  (Fig. 2).

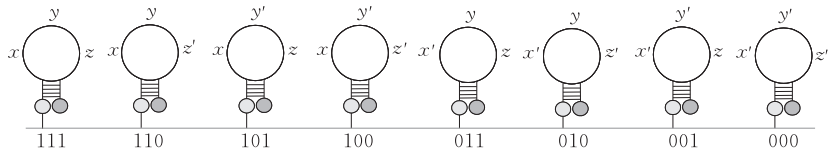


Fig. 2 Molecular Beacons' code

Molecular Beacon detailed code is shown in the Fig. 3. MB\_XXX in the figure stands for coding of Molecular Beacon, and the underscores is identification zone of Molecular Beacon (standing for low-ercase letters), the direction of 5′-3′ is the coding of  $x$  or  $x'$ ,  $y$  or  $y'$ ,  $z$  or  $z'$  in turn; Stalk of Molecular Beacon composed by 6 bps complementary base at both ends (expressed in capital letters). Primer is the primers of polymerase extension reaction, it is complementary strand of DNA ( $\{5'-ATATAC-3'\}$ ) of Molecular Beacon in the state of open loop in the 3′ ends. Choose fluorescent green (Fluorescent Green ABI) as fluorescent group of Molecular Beacon, and choose DABCYL as quenching group of Molecular Beacon. Finally, use carbon atom with 5′-Thiol-Modifier as connection arm ( $5'-HS-C_6-T_{10}-GAATTC-\dots-3'$ ), and make all Molecular Beacons on the order from right to left to be fixed in the surface of carrier.

Name	Sequence (5′-3′)
MB_000	ATATAC - ttccgcattg - ttatatacatg - ttggagcccg - GTATAT
MB_001	ATATAC - ttccgcattg - ttatatacatg - ctctacagtg - GTATAT
MB_010	ATATAC - ttccgcattg - tccaatctgt - ttggagcccg - GTATAT
MB_011	ATATAC - ttccgcattg - tccaatctgt - ctctacagtg - GTATAT
MB_100	ATATAC - ttccgcattg - ttatatacatg - ttggagcccg - GTATAT
MB_101	ATATAC - ttccgcattg - ttatatacatg - ctctacagtg - GTATAT
MB_110	ATATAC - ttccgcattg - tccaatctgt - ttggagcccg - GTATAT
MB_111	ATATAC - ttccgcattg - tccaatctgt - ctctacagtg - GTATAT
Primer	ATATAC

Fig. 3 Encode table

Now let's carry out the step 2. Given paradigm for the first item( $x \vee \bar{y}$ ), we add  $x$  and  $y'$ 's complementary strands of PNA ( $\bar{x}$  and  $\bar{y}'$ ) in the surface to hybridize. The identification zone of Molecular Beacon met this item must contain half-bred PNA molecule ( $\bar{x}$  and  $\bar{y}'$ ), such as  $\{(1,1,1),(1,1,0),(1,0,1),(1,0,0),(0,0,1),(0,0,0)\}$  in the Fig. 4; The identification zone of Molecular Beacon not met this item must not contain half-bred PNA molecule, such as  $\{(0,1,1),(0,1,0)\}$  in the Fig. 4.

After complementary strands of PNA ( $\bar{x}$  and  $\bar{y}'$ ) have hybridized with Molecular Beacon, heating the surface untied double-stranded of stem. At

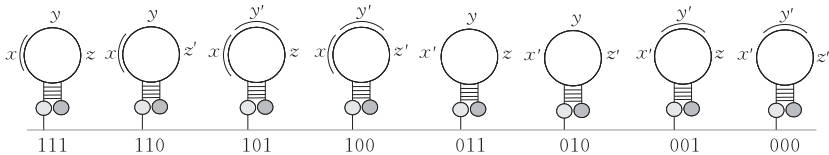


Fig. 4 The first item of paradigm

this moment, Molecular Beacon converts from the closed-loop into the open-loop and becomes linear molecule (Fig. 5).

Adding primer ( $\{5'-ATATAC-3'\}$ ) and polymerase in the surface, the primer is hybridized in the 3′ of Molecular Beacon, and then react polymerase extension reaction under polymerase's effect. Corresponding to Molecular Beacon met this normal form, its identification zone has the half-bred PNA chain, and PNA skeleton of the peptide prevents the reaction, so, EcoRI's recognition site is still single chain after polymerase extension reaction. Corresponding to Molecular Beacon ( $\{(0,1,1),(0,1,0)\}$ ) not met this normal form, because of its loop not having complement PNA strand, the primer is extended to spacing sequence, and makes EcoRI's recognition site become double-strand under polymerase's effect. At this time, add EcoRI in the surface, and the recognition site is identified and digested, so that the Molecular Beacons not met this item can be removed in the surface (Fig. 6).

After the step, the first item's the solution to meet the given paradigm is  $\{(1,1,1),(1,1,0),(1,0,1),(1,0,0),(0,0,1),(0,0,0)\}$ .

Step 3: Heating the chain, clean and remove the hybridized complement PNA strands ( $\bar{x}_i$  or  $\bar{y}'$ ). Then, anneal makes Molecular Beacon be shaped again(Fig. 7).

Repeat the following operation, for the second item( $\bar{x} \vee z$ ) of the given paradigm, Molecular Beacon met its first and second items is  $\{(1,1,1),(1,0,1),(0,0,1),(0,0,0)\}$  (Fig. 8).

For the third item( $\bar{y} \vee \bar{z}$ ) of the given paradigm, all Molecular Beacons met all items of the given paradigm are:  $\{(1,0,1),(0,0,1),(0,0,0)\}$  (Fig. 9).

Step 5: Heating the surface directly. Molecular Beacon converts from the closed-loop into an open-loop and the fluorescence. Use LSCM for solution detection (Fig. 10).

The fluorescence information on the surface illuminates that it can be satisfied for the given paradigm, and the ultimate solution is  $x=1,y=0,z=1$ ,  $x=0,y=0,z=1$  and  $x=0,y=0,z=0$ .

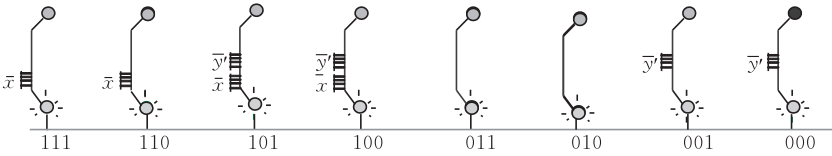


Fig. 5 Molecular Beacon converts from the closed-loop into the open-loop

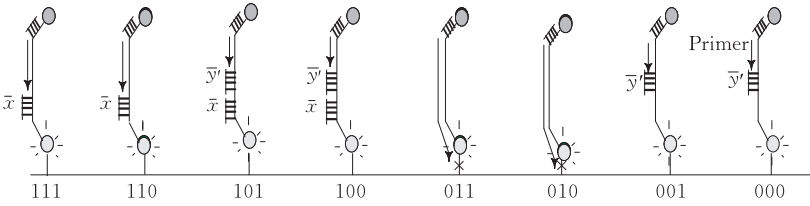


Fig. 6 EcoRI degrades Molecular Beacon not met the first item

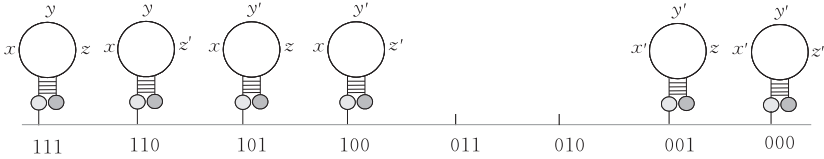


Fig. 7 Molecular Beacon met the first item of paradigm

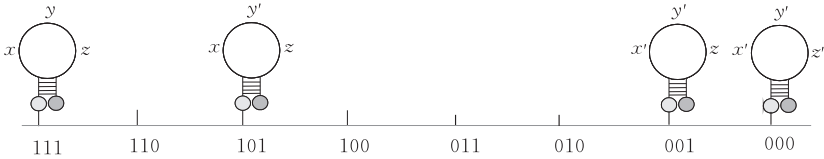


Fig. 8 Molecular Beacon met the first and the second items of the paradigm

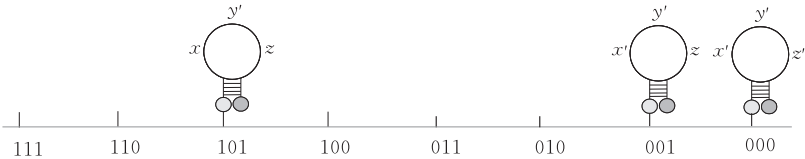


Fig. 9 Molecular Beacons met all items of the given paradigm

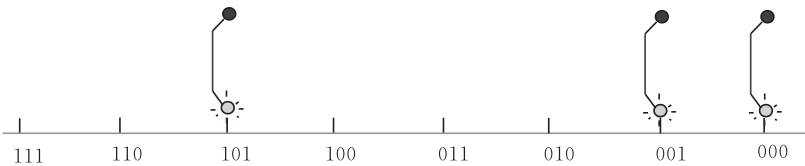


Fig. 10 The final solution's detection

5 Conclusion

In this paper, we used hybrid between Molecular Beacon and PNA to solve SAT Problem. All possible solutions of SAT Problem were encoded in the identification zone of Molecular Beacon. With hybridization between Molecular Beacon and PNA molecules, the Molecular Beacon satisfying the given paradigm, “protected” by complement PNA strands of restriction variable, can’t be identified and degraded by EcoRI following polymerase extension reaction, while the Molecular Beacon not

satisfying the given paradigm, not “protected” by complement PNA strands, can be degraded by EcoRI and removed from the surface following polymerase extension reaction. When all the items of the paradigm have been considered, Molecular Beacon left on the surface is the solution of the given problem, and then use fluorescence formed by the change of Molecular Beacon’s configuration to read solution directly, and do not have to observe and record intermediate results of the calculation. This reading method is simple, reliable and enriched testing methods of final results of DNA

computing. This paper has tried to use Molecular Beacon differential hybrid with target sequence, and the PNA molecule's unique nature to solve problems in the field of DNA computing, such as biochemical reactions' easy fluff, the end result difficult to detect, and so on. Molecular Beacon is highly sensitive, specific and specific hybrid between Molecular Beacon and PNA, without the degradation of DNA, and prevents polymerase's effect. These roles have been now widely used in Molecular Beacon biology, and to explore the applications in the field of DNA computing will certainly promote the development of the field.

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