

# 基于压电基因传感器的 DNA 计算

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**摘 要** 压电基因传感器是一种新型的生物传感器,它把压电传感器的灵敏性和 DNA 杂交反应相结合.与传统的基因检测技术相比,它具有结构简单、无需标记、检测时间短、检测信号易处理等特点.将它用于分子运算,与常规的 DNA 芯片相比,它的检测结果更易于进行自动化处理,因此便于构建大规模的分子运算机器.文中在压电基因传感器和新兴学科 DNA 计算的基础上,给出了解决 0-1 规划问题新的 DNA 计算方法,并指出以前两种基于表面 DNA 计算在解决这一问题时的不足.与以往的 DNA 计算方法相比其输出的是电信号,因此具有操作易自动化、识别解更方便和高信息量的优点.与使用常规 DNA 芯片的表面 DNA 计算相比,使用压电基因传感器进行 DNA 计算可以克服可行解识别困难的问题.压电基因传感器技术有望成为新的分子运算工具,可作为构建自动化的 DNA 计算机的基础.

**关键词** 压电基因传感器; DNA 芯片; DNA 计算; 0-1 规划问题; DNA 计算机

**中图法分类号** TP301

## DNA Computation Based on Piezoelectric Genosensor

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**Abstract** Piezoelectric genosensor is a new type of biosensor, which combines the sensitivity of piezoelectric sensor and DNA hybridization reaction. Compared with traditional gene assay technology, it has the simple construction, label-free feature, time-saving detection speed, and conveniently processed information. When used in DNA computing, compared with conventional DNA chip, its information is easier to process automatically. Thus it can be used conveniently to construct an automatic computing machine. Based on the piezoelectric genosensor and DNA computing theory, a new DNA computing method to solve 0-1 programming problem is proposed in this paper. Compared with other DNA computing methods, it has more significant advantages due to its electric signal output, such as massive parallel of obtaining and managing information, automatically processed signal, and label-free solution detection, etc. It also can overcome some problems, such as solution distinguishing, when carrying out DNA computing with conventional DNA chip. The piezoelectric genosensor can be used as a potential DNA computing chip to construct a DNA computer.

**Keywords** piezoelectric genosensor; DNA chip; DNA computing; 0-1 programming problem; DNA computer

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1 Introduction

With the development of modern biotechnology and electronics technology, biosensor has become a brand-new high-technology field yet. Piezo-electric genosensor is a new type of biosensor. Compared with traditional gene assay technology, it has the features of simple structure, label-free property, and fast detection speed<sup>[1]</sup>. Based on the piezoelectric and reverse piezoelectric effect of some crystals, this sort of biosensor is constructed. Nowadays, there has been great interest in the use of microgravimetric quartz crystal microbalance (QCM) as a promising candidate for biosensor applications and the QCM has demonstrated its potential for detection of DNA hybridization. When the ssDNA probes anchored on the surface of QCM hybridize with their complementary ssDNA strands, the weight on the surface of the QCM will increase. Attributed to its sensitivity to mass change, the frequency of the QCM will decrease. The relation between mass change ( $\Delta m$ ) and frequency change ( $\Delta f$ ) can be rendered as  $\Delta f = -k f_0^2 \Delta m / A$ . In the equation, the  $k$  is a constant related to the material which is used to make QCM, and the  $f_0$  is the frequency of the QCM before hybridization reaction. The  $A$  is the reaction area, and the “-” means that the increasing of mass will cause decreasing of frequency<sup>[2]</sup>. Although the QCM is sensitive to sub-nanogram lev-

els of mass change, in order to widen the application of the technique, various methods for improving the detection limit of the QCM have been developed. Recently, the development of amplification for the sensing process of dsDNA assembly has been reported in some research work<sup>[3]</sup>. In ref. [3], Peng et al. used actinomycin D-functionalized magnetic nanomicrospheres as microgravimetric amplifying labels. Actinomycin D (ActD) is one of the important anticancer antibiotics, which intercalates preferentially into the (dG, dC) region on a DNA duplex and generates a wide variety of biochemical and pharmacological effects to interfere with gene replication and transcription. These nanomicrospheres can interact with dsDNA formed by hybridization which is anchored on the gold film electrode of an electrochemical quartz crystal microbalance (EQCM). ActD acts as a guide that leads heavy microspheres onto the dsDNAs at the EQCM film. And a magnetic separation shelf could separate unreacted microspheres conveniently. The modification and DNA hybridization at EQCM electrodes were examined by microgravimetric and electrochemical methods. In this way, an outstanding change in frequency decrease has been monitored owing to the mass increase on the EQCM electrodes (Fig.1(a)). Except the method proposed in ref. [3], avidin-biotin interaction is used to amplify the hybridization signal in this paper (Fig.1(b)).

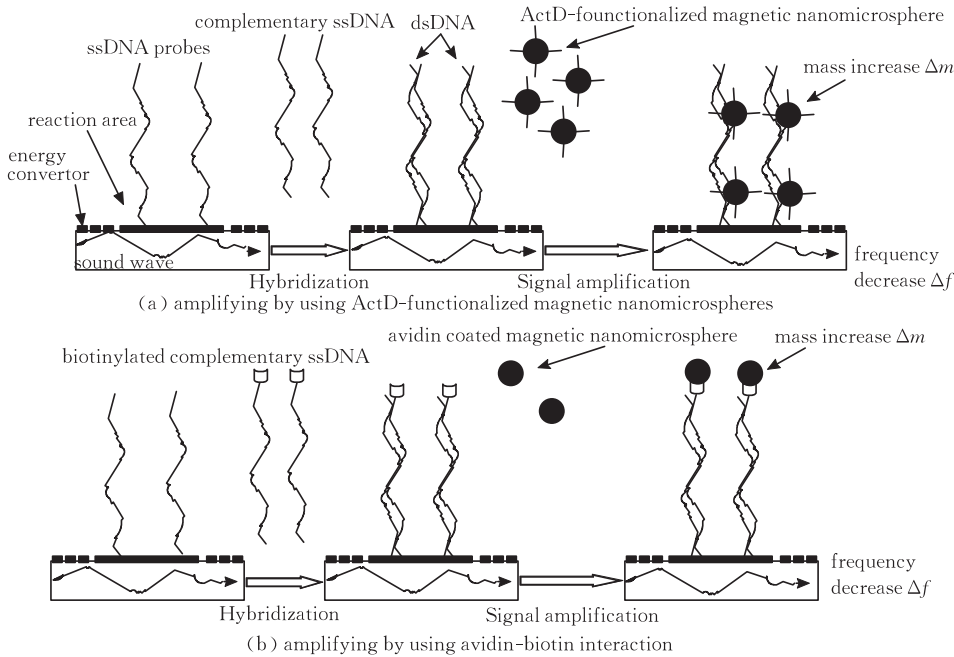


Fig. 1 Signal amplification

Since Adleman<sup>[4]</sup> demonstrated how standard methods of molecular biology could be used to solve a hard computational problem, the research of DNA computing and DNA computer have been grown in an amazing speed. So far, many molecular computing models have been brought forward based on DNA molecule, enzyme and biotechnology. For instance Sakamoto offered a model to solve an SAT problem through DNA's hairpin structure elaborately<sup>[5]</sup>. By using POA to generate DNA sequence, Ouyang designed the DNA molecular database for DNA computation, and based on these sequences they had set up an algorithm for the maximal clique problem<sup>[6]</sup>. In 2000, Liu et al. proposed the surface-based DNA computation model to solve SAT<sup>[7]</sup>. Shortly after, the work group led by Professor Shapiro in Weizman Institute brought forward an automatic DNA computer model for diagnosing and curing diseases<sup>[8-9]</sup>. Some DNA computations are based on ingenious molecular biology techniques. For example, Fengyue and Zhixiang presented a novel DNA computation model which combine the surface-based detecting technique and molecular computing in tubes<sup>[10]</sup>. In this paper, the concept of performing DNA computation with piezoelectric genosensor is introduced. Compared with Yin and Zhang's DNA computing model<sup>[10-11]</sup>, this sort of surface-based DNA computation method can be used to solve more complicated problems in operational researches, not only 0-1 programming problem. And the biological procedure can be more feasible.

## 2 DNA Algorithm of 0-1 Programming Problem

The 0-1 programming problem is a special form of an integer programming problem, in which the value of variable  $x_i$  is only 0 or 1. In this condition,  $x_i$  can be referred to as either a "binary" or "0-1" variable. The general form of 0-1 programming problem is:

$$\begin{cases} \max(\min) z = c_1 x_1 + c_2 x_2 + \cdots + c_n x_n, \\ a_{11} x_1 + a_{12} x_2 + \cdots + a_{1n} x_n \leq (=, \geq) b_1 \\ a_{21} x_1 + a_{22} x_2 + \cdots + a_{2n} x_n \leq (=, \geq) b_2 \\ \cdots \\ a_{m1} x_1 + a_{m2} x_2 + \cdots + a_{mn} x_n \leq (=, \geq) b_m \\ x_1, x_2, \cdots, x_n = 0, 1; a_{ij} \text{ are integer;} \\ b_j \text{ are nonnegative integer} \\ (i=1, 2, \cdots, m; j=1, 2, \cdots, n) \end{cases} \quad (1)$$

0-1 programming problem is an important

problem in operation research and has very wide-spread application. A wide variety of algorithms have been written to solve the 0-1 programming problem including methods of exhaust algorithm, invisible enumeration, and others. The computing time of these methods increases exponentially with problem size. Otherwise, 0-1 programming problem and the satisfiability problem are both closely related, and 0-1 programming problem is a generalization of the satisfiability problem. In this paper the DNA algorithm of 0-1 programming problem based on piezoelectric genosensor is proposed. This algorithm is an improvement of traditional surface based DNA computing, and used to solve a special form of 0-1 programming problem:

$$\begin{cases} \max(\min) z = c_1 x_1 + c_2 x_2 + \cdots + c_n x_n, \\ a_{11} x_1 + a_{12} x_2 + \cdots + a_{1n} x_n \leq (=, \geq) b_1 \\ a_{21} x_1 + a_{22} x_2 + \cdots + a_{2n} x_n \leq (=, \geq) b_2 \\ \vdots \\ a_{m1} x_1 + a_{m2} x_2 + \cdots + a_{mn} x_n \leq (=, \geq) b_m \\ x_1, x_2, \cdots, x_n, a_{ij} = 0, 1; \\ c_i, b_j \text{ are nonnegative interger} \\ (i=1, 2, \cdots, m; j=1, 2, \cdots, n) \end{cases} \quad (2)$$

The following algorithm was designed to solve the 0-1 programming problem corresponding to (2):

Step 1. Generate all possible solutions, consisted of all possible combinations of 0 and 1, for the given special 0-1 programming problem described in (2).

Step 2. Delete the non-feasible solutions in all possible solutions by using the constraint equations.

Step 3. Keep the remnant solutions.

Step 4. Repeat steps 2 and 3. After all of the constraint equations have been applied, we can eliminate all of the non-feasible solutions, and obtain all of the feasible solutions to the given special 0-1 programming problem.

Step 5. Compute the value of target function for each feasible solution, and compare those values. Finally we can obtain the optimum solutions to the given problem.

Corresponding to above algorithm, the DNA computing procedure was designed as follow:

Step 1. Generate all kinds of different oligonucleotides that represent the variables of given 0-1 programming problem.

Step 2. Based on Watson-Crick principle, complementary DNA sequences will hybridize. The DNA database of all combinations represen-

ting the variables are 0 or 1 is obtained.

Step 3. By modern molecular biological technology, the combinations satisfying the constraints or not can be distinguished. Eliminate unsatisfying combinations and keep satisfying ones.

Step 4. Repeat Step 3 and eliminate other unsatisfying combinations (The unsatisfying combinations produced in last Step 3 are not considered). In this way all the unsatisfying combinations can be eliminated, and all the feasible solutions to given problem can be judged.

Step 5. Calculate the value of object function corresponding to every feasible solution, and judge the optimum solution.

When  $a_{ij}$  are nonnegative integer,  $a_{ij}x_j$  are re-presented with  $\sum_j^{a_{ij}}x_j$ .

3 DNA Solution to 0-1 Programming Problem Based on Piezoelectric Genosensor

Compared with the solution to 0-1 programming problem described in ref. [11], the new DNA solution to the same problem is presented.

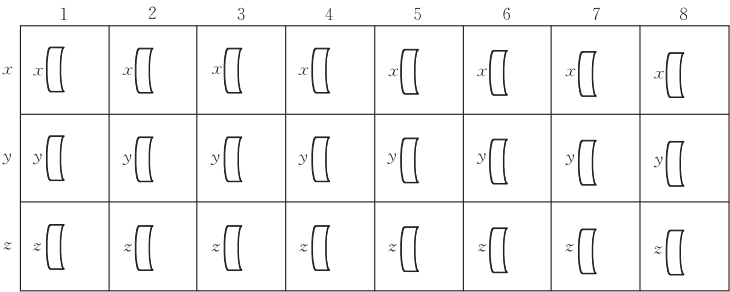


Fig. 2 3×8 array of piezoelectric genosensors

Step 2. Mix the oligonucleotides representing  $\bar{x}, \bar{y}, \bar{z}$  and  $\bar{x}', \bar{y}', \bar{z}'$  (unbiotinylated) in proper concentration. The mixture is added to the reaction area on the surface of sensor array for hybridizing with surface-immobilized DNA (42°C, 6h are universal reaction condition). After reaction, the reaction areas are washed with proper buffer in a strict condition and unhybridized oligonucleotides are removed. After this procedure, all the possible solutions are produced (Fig. 3). Then take down the frequency of every piezoelectric genosensor.

Step 3. Add avidin-coated magnetic nanomicrosphere to the reaction areas. It will interact with 5' ends biotinylated oligonucleotides, then the mass on the surface of sensor increase and cause decrease of frequency of sensor. Wash with proper buffer and remove unreacted magnetic nanomicrosphere and take down the sensor frequency at this

$$\min u = 2x + y + 3z,$$
$$\begin{cases} x + z \leq 1 \\ x + y + z \geq 2 \\ y + z \leq 1 \\ x, y, z = 0, 1 \end{cases}.$$

The computing process is described in detail as follow:

Step 1. Construct 3 kinds of different oligonucleotides. Their sequences are AACCTGGT, ACGATAGC and AGAGTCTC which represent the variables  $x, y, z$ . In same time the complementary sequences TTGGACCA, TGCTATCG and TCTCAGAG are constructed, which correspond to  $\bar{x}, \bar{y}, \bar{z}$  and  $\bar{x}', \bar{y}', \bar{z}'$ . Then, the oligonucleotides representing variables  $x, y, z$  are 5' ends mercaptohexyl-modified and the oligonucleotides representing  $\bar{x}, \bar{y}, \bar{z}$  are 5' ends biotinylated. Immobilize 5' ends mercaptohexyl-modified oligonucleotides (representing  $x, y, z$ ) on the surface of piezoelectric genosensor coated with gold. The sensor array is 3×8, which is illustrated in Fig. 2. In order to control the results of computing process, controlled groups contained the same sensor array are very necessary.

time. Then compare the value of frequency with the value taken down in Step 2. As illustrated in Fig. 3, the positive result means that the sensor is attached with magnetic nanomicrosphere and cause frequency decrease (the dark dots in Fig. 3 represent attached magnetic nanomicrosphere). The value of corresponding variable is 1, and there are no attached magnetic nanomicrosphere means the value of corresponding variable is 0.

Step 4. Results analyzing: For the first constraint  $x + z \leq 1$ , the frequency of sensor in columns 1 and 3 which representing the variables  $x, z$  decreased markedly. It means that the values of  $x, z$  are 1 simultaneously. These solutions did not satisfy the constraint, and the solutions in column 2, 4, 5, 6, 7 and 8 satisfy the constraint. Based on same principle, the solutions in column 2 and 5 satisfy the second constraint  $x + y + z \geq 2$ , and the

solutions satisfying the third constraint locate in column 2. Then the solutions satisfying all three constraints were obtained. Compare the value of object functions and get the optimum solution. For the given problem, the feasible solutions locate on-

ly in column 2. The variable value (1,1,0) corresponding to column 2 is the optimum solution, and the minimal value corresponding to object function is 3.

	1	2	3	4	5	6	7	8
$x$								
$y$								
$z$								

Fig. 3 When added magnetic nanomicrosphere, solution space came into being (The values corresponded to  $x,y,z$  are 1(1,1,1),2(1,1,0),3(1,0,1),4(1,0,0),5(0,1,1),6(0,1,0), 7(0,0,1) and 8(0,0,0) respectively)

To solve the same problem described in ref. [11], performing computation with piezoelectric genosensor can be simpler. And the output signal of piezoelectric genosensor is electronic and can be processed by a computing machine. Based on this, constructing an automatic computing machine become possible. But we must emphasize that the method mentioned here and in ref. [11] can not be carried out in practice. Because the DNA sequence on the surface of every sensor or chip is not a single one, labeled and unlabeled complementary DNA will hybridize. Unexpected hybridization can not be avoided, and the solution space will not come into being. In order to overcome this, based on the method mentioned in ref. [12] a new solution is presented. But in ref. [12] they link 3 kinds of different fluorescence dyes such as Red, Green and Blue to each one DNA strand from the top down. After adding positive and negative complement link with fluorescence quenchers and observed by laser confocal microscope, the solution was supposed to be determined. Actually, this algorithm can not be carried out because it is considerable difficult to distinguish different colors in one address. By using piezoelectric genosensor the given 0-1 programming problem can be solved, and the computing procedure is more feasible.

The computing procedure is described as follow.

For an equation set that contain  $m$  equations and  $n$  variables  $x_1,x_2,\cdots,x_n$ :

Step 1. The step can be divided into two sub steps. Firstly, generate  $3n$  kinds of different oligonucleotides, and divide them into 3 groups. Let the  $n$  kinds of different oligonucleotides in the first

group denote the variables  $x_1,x_2,\cdots,x_n$ , the  $n$  kinds of different oligonucleotides in the second group denote the variables  $x'_1,x'_2,\cdots,x'_n$ , the  $n$  kinds of different oligonucleotides in the third group denote the variables  $\bar{x}_1,\bar{x}_2,\cdots,\bar{x}_n$  which are complementary sequences of first group.

When generating oligonucleotides, proper encoding strategy must be adopted to avoid unwanted hybridization and forming of hairpin structure. The oligonucleotides of first and second group hybridize means that the value of variable  $x_i$  is 1, the oligonucleotides of second group don't hybridize with others means that the value of variable  $x_i$  is 0.

In the second sub step, the data base is constructed with the  $2n$  kinds of oligonucleotides in the first and second group. Construct  $2^n$  different combinations of the  $2n$  kinds of different oligonucleotides and each combination shall include the oligonucleotides corresponding to the  $n$  different variables. Then we will obtain  $2^n$  kinds of different DNA strands which are made by  $T_4$  ligation enzyme and represent all the possible solutions. These oligonucleotides are 5' ends mercaptohexyl-modified and immobilized on the surface of piezoelectric genosensor coated with gold.

Step 2. Record the frequency of every piezoelectric genosensor before hybridization, and then add proper dose of oligonucleotides which represent the value of constraint equation to the reaction area. After hybridization, add the ActD-function-alized magnetic nanomicrospheres. Remove unreacted magnetic nanomicrospheres with a magnetic separation shelf and record the frequencies of piezoelectric genosensors at this time. Then record the

frequency decrease of every piezoelectric genose-nor. In addition, we define that the degree of fre-quency decrease is 1 when one oligonucleotide seg-ment hybridizes, 2 when two oligonucleotide seg-ments hybridize, 3 when three segments hybridize. According to ref. [3], by using ActD-functional-ized magnetic nano-microspheres as microgravimet-ric amplifying labels the sensitivity of the piezoelec-tric genosensor can attain this.

Step 3. Repeat step 2, take down all the so-lutions that satisfy constraint equations.

Step 4. Keep the solutions satisfying the equation set, eliminate unsatisfying solutions. Cal-culate the target function's value for each feasible solution, and compare those values. Finally we can obtain the optimum solutions to the given prob-lem.

The same problem is solved as follow:

Step 1. Construct 3 kinds of different oligo-nucleotides of first group. Their sequences are AACCTGGT, ACGATAGC and AGAGTCTC which represent the variables  $x, y, z$ . Then, con-struct the second group oligonucleotides which se-quences are CCAAGTTG, GTTGGGTT and AGCTTGCA. They represent variables  $x', y', z'$ . The oligonucleotides of third group are comple-mentary sequences of first group, represented as  $\bar{x}, \bar{y}, \bar{z}$ . Construct series-connection of first 6 kinds of oligonucleotides, which will produce  $2^3 (= 8)$  kinds of combinations representing the solution

space. These 8 kinds of DNA sequences are 5' ends mercaptohexyl-modified and immobilized on the surface of piezoelectric genosensor coated with gold (Fig. 4(a)).

Step 2. For the first constraint  $x + z \leq 1$ , the oligonucleotides representing  $\bar{x}, \bar{z}$  (complementary sequence of  $x, z$ ) are added onto the reaction areas to hybridize with the 8 kinds of DNA sequences which have been immobilized on the surface of sen-sor. After reaction, the reaction areas are washed with proper buffer in a strict condition and unhy-bridized oligonucleotides are removed. Take down the frequency of each sensor at this time. Add the ActD-functionalized magnetic nanomicrospheres. Remove unreacted magnetic nanomicrospheres with magnetic separation shelf and keep the frequencies of piezoelectric genosensor. Then record the fre-quency decrease of every sensor, and compare these frequencies with the frequencies taken down after hybridization. If the degree of frequency decrease is 1 or 0, the solution corresponding to immobi-lized DNA sequences satisfy the constraint equation (For the given problem, the numbers correspond-ing to feasible solutions are 0, 1, 2, 3, 4, 6. Fig. 4 (b)). Then, heat the products to unwrap the double-strands, and wash away all of the comple-ment oligonucleotides. Remove magnetic nanomi-crospheres with magnetic separation shelf. In this step, the solutions corresponding to the number 5 and 7 were eliminated.

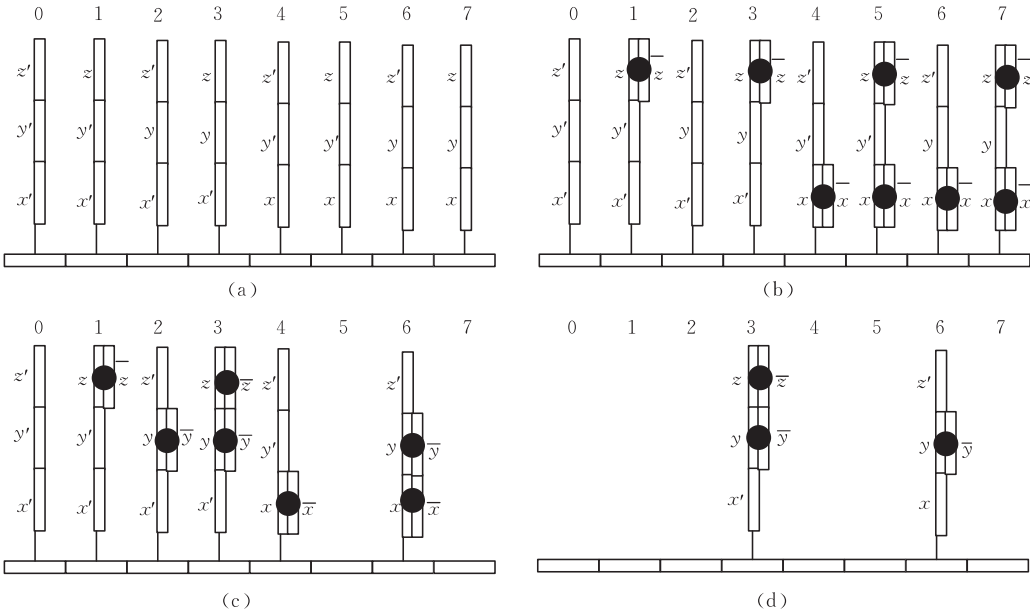


Fig. 4 The schematic diagram of computing procedure (The dark dot symbolizing the magnetic nanomicrosphere attached to ssDNA)

Step 3. Consider remnant two constraint equations, and repeat step 2. For second constraint  $x+y+z \geq 2$ , the oligonucleotides representing  $\bar{x}$ ,  $\bar{y}$ ,  $\bar{z}$  (complementary sequence of  $x$ ,  $y$ ,  $z$ ) are added onto the reaction areas to hybridize with the remnant 6 kinds of DNA sequences. If the degree of frequency decrease is 2, the solution corresponding to immobilized DNA sequences satisfy the constraint equation (For the given problem, the numbers corresponding to feasible solutions are 3, 6. Fig. 4(c)). The third constraint equation can be processed in the same way.

Step 4. Calculate the values of object functions according to feasible solutions, and judge which the optimum solution is. For the given problem, the feasible solution corresponds to number 6 which represents the solution (1, 1, 0). It is the optimum solution, and the minimal value of object function is 3 (Fig. 4(d)).

## 4 Discussion

In this paper, a new surface-based DNA algorithm to 0-1 programming problem was proposed. By using piezoelectric genosensor, an automatic DNA computing device could be constructed. Compared with other DNA computing model to 0-1 programming problem<sup>[11-12]</sup>, this DNA computer model is more feasible and can be used to solve more complicated problems in operational researches. Compared with traditional surface-based DNA computing model, this DNA computation system can run more automatically. It is suggested that by using piezoelectric genosensor and combined with electronic computer an automatic DNA computer could be constructed. Although the computing procedure of this DNA computation model have not been executed substantially so far, according to other's

experience<sup>[3]</sup> the algorithm is fairly feasible.

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