A Personification Heuristic Genetic Algorithm for Digital Microfluidics-based Biochips Placement

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Abstract

A personification heuristic Genetic Algorithm is established for the placement of digital microfluidics-based biochips, in which, the personification heuristic algorithm is used to control the packing process, while the genetic algorithm is designed to be used in multi-objective placement results optimizing. As an example, the process of microfluidic module physical placement in multiplexed in-vitro diagnostics on human physiological fluids is simulated. The experiment results show that personification heuristic genetic algorithm can achieve better results in multi-objective optimization, compare to the parallel recombinative simulated annealing algorithm.

Keywords*: personification heuristic algorithm*, g*enetic algorithm*, d*igital microfluidics-based biochips*, *placement*

1. Introduction

Digital microfluidics-based biochips, which are widely used in more and more different fields, such as analytical chemistry, clinic diagnosis, biology manufactory, environmental monitor, and military [1-3]. As biochips are adopted for complex procedures in molecular biology, the design complexity of digital microfluidics-based biochips is expected to increase due to the need of multiple and concurrent assays on a biochip. The international technology roadmap for semiconductors (ITRS) clearly points out that the integration of electro-biological devices is one of the major challenges of system integration beyond 2009. The placement of digital microfluidics-based biochips is one of the key points in the chip design, through which the physical position of each biochemical analysis operation can be found with the smallest biochip area and the shortest completion. The algorithm for the placement has been paid great attention by different groups. Su and Chakrabarty presented a unified synthesis and placement flow based on parallel recombinative simulated annealing. They used the list-scheduling algorithm for scheduling and a greedy placement algorithm for physical placement [4-6]. The placement is somehow not very compacted and cannot meet all design specifications. While the T-tree formulation developed by Yuh etc. from Taiwan University [7, 8] shows better results with a tree-based topological representation, but the completion time is not so good due to the large amount of calculations needed and that is time-consuming.

The placement of digital microfluidics-based chip is an optimization of multi-objectives. In this article, we combine personification heuristic algorithm with genetic algorithm to solve the placement problem.The results showed a better biochip area and shorter completion time, compare to the parallel recombinative simulated annealing algorithm and T-tree.

2. The Placement of Microfluidic-based Biochips

The procedure of the placement of microfluidic-based biochips is shown as Figure 1. There are three inputs to the placement problem. The first one is the sequencing graph $G = \{V, E\}$ that represents the protocol of a bioassay, where $V = \{v_1, v_2, . . . , v_m\}$ represents a set of m assay operations and $E = \{(v_i , v_j), 1 \le i, j \le m\}$ denotes the data dependencies between two assay operations; i.e., the *precedence constraints*. We may need at most one storage unit for each edge in G to store the intermediate data between two data-dependent operations . The second one is the microfluidic module library that contains the basic modules for biochips. Each

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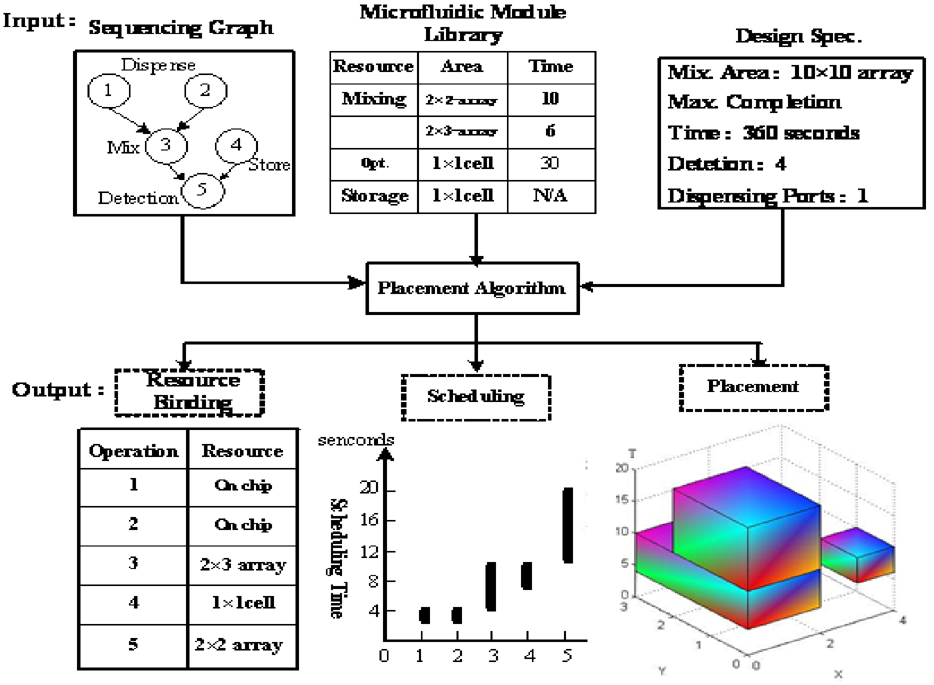
basic module is characterized by its functionality (i.e., mix, dilution, etc.) and parameters (i.e., width, height, and operation duration). The third one is the design specification, including:

(1) the fixed architecture (such as 10×10 array) and limited assay completion time (such as 360 seconds)

(2) the maximum number of instances for each type of non-reconfigurable devices(such as detector and dispensing ports); that is, the resource constraints.

The placement of modules on the microfluidic array can be modeled as a 3-D packing problem. Each microfluidic module is represented by a 3-D box, the base of which denotes the rectangular area of the module and the height denotes the time-span of its operation. The microfluidic biochip placement can now be viewed as the problem of packing these boxes to minimize the total base area, while avoiding overlaps.



Resource	Area	Time
Mixing	2×2-array	10
	2×3-array	6
Opt.	1×1cell	30
Storage	1×1cell	N/A

Mix. Area : 10×10 array
Max. Completion
Time : 360 seconds
Detetion : 4
Dispensing Ports : 1

Operation	Resource
1	On chip
2	On chip
3	2×3 array
4	1×1cell
5	2×2 array

Figure 1. Procedure of the Placement Problem of Biochips

3. Personification Heuristic Genetic Algorithm

Personification heuristic genetic algorithm is formulated based on the simulation of natural optimization law, which has some advantages of solving the optimization of the 3-D packing problems, especially when for the large-scale problems with great complexity. In order to obtain a more compact placement layout, we combine the personification heuristic algorithm with the genetic algorithm. Personification heuristic algorithm is used to control the placement of the modules, and then optimize the placement results of the multiple objectives by genetic algorithm in order to achieve the goal of smallest microfluidic array area and shortest completion time. The key points of genetic algorithm are the design of encoding and the selection of the fitness function [9].

3.1. Personification Heuristic Algorithm

As we know, the efficiency of personification heuristic application was firstly proved on the three-dimensional packing problem [10]. In the construction of buildings, workers always set a brick as the reference of height when walls are built. The height of other bricks cannot exceed that of the reference brick until no other brick can be build in, when new height reference brick need to be set. In addition, this enlightens the researchers to set “reference bricks” in both horizontal and vertical directions as the guide of the module placement in digital microfluidics-based biochips. The positions of digital microfluidic modules can be recorded and found by the reference pointed set beforehand in the placement procedure and no special request of placement results needed as in other designs. Thus, the whole placement of the digital microfluidic modules can be finished with much more flexibilities by the setting of the reference lines.

3.1.1. Selection of Placement Point

As shown in Figure 2, the microfluidic modules of the biochip is embedded into a three dimensional coordination, in which the upper left corner of the bottom set as origin, and length, width, height as *x, y, z,* respectively. Based on the experiences, the current module to be placed must be as close as possible to the axis of coordination, or to the last module placed, therefore, we designed a method to record the point that can be placed in which the upper-left corner coordinates of the bottom are used as the coordinates of the digital microfluidic modules.

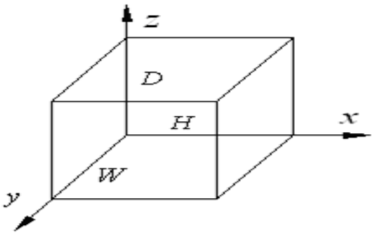


Figure 2. Coordinate System

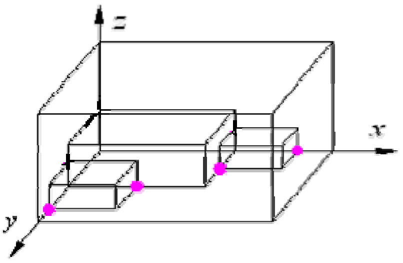


Figure 3. Available Points

The starting and ending time of each digital microfluidic modules are determined by its architecture-level scheduling, namely the position of the module on the *z*-axis. Suppose that digital microfluidic module with the scheduling sequence of (b_1, b_2, …, b_n) starts its implementation at time t=0, the length of digital microfluidic module b_i along the *x, y,* and *z*-axis will be l_i', w_i', h_i'. The first digital microfluidic module can be placed in the point of (0, 0, 0), and thus the second one can be located into the two possible positions: (l_1', 0, 0) or (0, w_1', 0), suppose the second digital microfluidic module choose the point of (l_1', 0, 0), then the point of (l_1', 0, 0) should be delete from the possible positions list for the third module, and another two point (l_1'+ l_2', 0, 0) and (l_1', w_2', 0) need to be added so that the third module can be put into one of the three positions: (0, w_1', 0), (l_1'+ l_2', 0, 0) and (l_1', w_2', 0). Therefore, if the digital microfluidic module located into position (x, y, z), then position (x, y, z) need to be deleted from the possible position collection of module i+1, and another two positions (x+l_i', y, z) and (x, y+w_i', z) added, shown in Figure 3.

3.1.2. Calibration of the Reference Line

In the placement layout of digital microfluidic-based biochips, there are maximum limits on the total completion time and the area of microfluidic arrays, i.e. the three –dimensional coordinates of the maximum length, width, height has their limits. Therefore, *two* reference lines set in the placement layout: the reference line L_y for *y*-axis and the L_x for *x*-axis, respectively. Our module placement policy is determined as: place the digital microfluidic modules according to the scheduling sequences, for the module b_i, firstly, the possible locations are sorted by the *y* coordinates in increasing order, and the locations with same *y* coordinate are sorted by the *x* coordinates in increasing order; then, make the judge that if the digital microfluidic module b_i can be located into one of the locations sorted. Note that the intersection of digital microfluidic module b_i with other modules in the same coordinate plate must be avoid when located into position (x, y, z), and in the meantime, the condition of y+w_i'≤ L_y, x+l_i'≤ L_x must be satisfied. Place the module bi into the first possible position and update the collection of possible positions; if no position available, adjustment can be performed in either of the following two ways:

(1) If L_x<L, then increase the reference line of *x*-axis, and set the module as the horizontal reference module, and if L_y<L, increase the reference line of *y*-axis.

(2) If there is still no position available for the module after the reference line increased, postpone the operation of the digital microfluidic module and put the droplet into the storage unit temporarily, and process with priority when spare period available for the operation.

3.1.3. Personification Heuristic Algorithm Flow

In conclusion, 3D-placement algorithm process is given, the algorithm input is an orderly digital microfluidic module set B = {b_1, b_2,... , b_n}, where *T* represents scheduling end time of digital microfluidic modules, *I* represents orderly place point set. When *I* is updated, we should keep the order of I elements. If the current digital microfluidic module can be placed, the symbol *flag*=1, otherwise the *flag*=0. The time of placement is *t*, which is mainly used to find the *t* moment need to start of the layout of the module. The flow of placement algorithm is as follows:

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3D-placement (B).
$I$={(0,0,0)}，$L_y=L_x=0$，$t=0$;
for $t$=0 to $T$，and $B$ not null
 { $n$= the number of scheduling digital microfluidic module on $t$ moment ；
  for $i$=1 to $n$
   { flag=0;
    for $(x, y, z)\in I$
      if $b_i$ can be placed at $(x, y, z)$, and $x+l_i'\le L_x$, $y+w_i'\le L_y$, then
        { flag=1, exit; }
      if  flag=0, then
        if $L_x$=0 or $L_x=L$， then
          if $b_i$ can be placed at (0, $L_y$), then
            { $x$=0, $y=L_y$, flag=1, $L_y=L_y+w_i'$, $L_x=l_i'$; }
          else if $L_y<L$, then
              { $L_y=L$, $L_x=L$, $i=i-1$; }
     else
           { for $(x, y ,z)\in I$ and $x=L_x$, $y$=0
               if $b_i$ can be placed at $(x, y, z)$ and $y+w_i'\le L_y$, then
               { flag=1, $L_x=L_x+ l_i'$, exit；}
              if  flag=0, then
               { $L_x=L$, $i=i-1$; }}
    if  flag=1, then
      { place $b_i$ at $(x, y, z)$, $I=I/\{(x, y, z)\}$, translate $b_i$ along the x and y coordinate in
        decrease order, keep the translation coordinates $(x', y', z')$, $I=I\cup\{(x'+ l_i', y', z'), (x',
        y'+ w_i', z')$; }}
 add one to $z$ coordinate and $z\in I$;
 delete the already layout node form $B$ ;
 move forward the back node.}
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3.2. Encoding

The encoding of genetic algorithm in this paper consists of three parts for the resources binding, scheduling and placement, respectively, which determine the start time and end time of each operation, perform the distribution and placement for the operations needed on the microfluidic arrays, such as mixing operations, storage operations, dilution operations and observation [11]. Each chromosome consists of *k*+*m*+*n* genes, and each gene g(*i*)∈(0,1)(*i*∈(1, *k*+*m*+*n*)) represents the priority of the operation, where *k* represents the number of resources binding, *m* represents the number of total operations, *n* represents the number of operations need to be placed, which means the digital microfluidic module with higher priority will be placed firstly in the queue.

3.3. Fitness Function

In order to evaluate the quality of the placement layout, the optimization of two parameters need to be considered, the smaller area of the microfluidic arrays and the shorter completion time [12]. This is a typical multi-objective optimization issue. In this article, the adaptation values are obtained through the adaptive weights method, in which the weights are adjusted according to the adaptation of current generation to acquire the searching ability of positive direction, and the valuable information of current population is used to readjust the weights in each generation. The selective power of this method is in between of fixed-weight method and the random weight method. For a given chromosome *x*, the fitness function of self-adaptive weight is as follows:

$$f(x) = -w_1 A(x) - w_2 T(x) \tag{1}$$

$$w_1 = \frac{1}{A_{\max} - A_{\min}} \tag{2}$$

$$w_2 = \frac{1}{T_{\max} - T_{\min}} \tag{3}$$

Where $A(x)$ and $T(x)$ denote the area of microfluidic array with a given chromosome x and the total completion time; $A_{\max}$ and $A_{\min}$ are the maximum and minimum values of the placement layout area of current population; $T_{\max}$ and $T_{\min}$ are the maximum and minimum values of the completion time of all operations in current population.

3.4. Algorithm Implementation

The main steps of the personification heuristic genetic algorithm are as follows:

Step 1 : Initialization of genetic parameters: set the initial population size as PopSize; hereditary generation as G_n; crossover probablity as P_c; the ratio of chromosomes copied directly to next generation as TOP; the ratio of new individuals generated randomly as BOT;

Step 2 : generate PopSize initial possible solution with the priority-based encoding method, set k=1（k is the initial searching number);

Step 3 : decode each chromosome: perform the heuristic decoding for the first k genes to determine the area of microfluidic array and completion time; sort the first k+1 to k+m+1 genes to determine the scheduling order and calculate the start time, end time of each operation and the total time spent T(x) by all the operations under the conditions of resource constraint; place all the operations under the scheduling order used the personification heuristic algorithm to obtain the placement coordinates and the area of each operation A(x).

Step 4 : calculate the weight of self-fitness w_1、w_2, convert the target value of the current population into the fitness function value, and sort the chromosomes in descending order according to the fitness function value, save the best fitness function value into f(x), and the best chromosome into Placement；

Step 5 : judge the ending condition, if the condition met, go to step 11 (the ending condition here is k≤Gn; if not, go to the next step;

Step 6 : generate new individuals under the crossover probability Pc, the quantity of new individuals is PopSize×（1-TOP-BOT）；

Step 7 : generate PopSize×BOT new individuals according the coding principle randomly;

Step 8 : perform Topological sort and evaluation for the new individuals generated;

Step 9 : sort the PopSize×TOP chromosomes of the generation k together with the new ones by Fitness function value in increasing order, save the best into the Placement, and save the fitness value into Placefunction;

Step 10 : Set k=k+1, go to step 5;

Step 11 : Output the optimized Placement, algorithm ended.

4. Results and Analysis

In order to evaluate the performance of the personification heuristic genetic algorithm (PHGA), a simulation experiment based on the multiplexed in-vitro diagnostics was carried out under the environment of Visual C++ as described in reference [5] with the algorithm formulated here.

For the multiplexed in-virto diagnostics, we used the same design specifications (resource constraint) as Su and Chakrabarty [5]. We assumed that there is one reservoir/dispensing port for each type of samples and reagents and one optical detector for each enzymatic assay. First, we assumed that no defective cells exist. Table 1 summarizes the result of the multiplexed in-vitro diagnostics. Comparing with those obtained in reference [5], in which the Parallel recombinative simulated annealing algorithm (PRSA) were used in the three experiments, the results by personification heuristic genetic algorithm (PHGA) show great advantage in completion time and the biochip area. Column 1 lists the type of samples and reagents used in each example: S_1: blood plasma, S_2: blood serum, S_3: emiction, S_4: saliva; A_1: glucose inspection, A_2: lactic acid salt inspection, A_3: pyruvic acid salt inspection, A_4: glutamine inspection. For each example, we applied three different design specifications, as listed in column 2. For instance, an experiment with the scale of 9×9×100 means the maximum values of the bottom coordinate projection of *x* and *y* are 9, and the longest completion time of the experiment is 100 seconds. We report the resulting area (centimeter) and completion time (in seconds) used the algorithm PRSA and PHGA. As shown in this table, PHGA can meet all design specifications while PRSA cannot. More importantly, PRSA requires larger basal area and longer complete time than our algorithm.

Figure 4 shows the placement result of the example 1 shown in Table 1 with the 9×9×100 design specification.

Table 1. Comparison Experimental Result

Description	Design Spec.	PRSA		PHGA	
		Basal Area(cm)	Complete Time(sec)	Basal Area(cm)	Complete Time(sec)
Example 1: S_1, S_2, S_3 and S_4 are assayed with A_1, A_2, A_3 and A_4	9×9×100	9×9	98	9×8	74
	8×8×120	10×9	117	7×5	102
	7×7×140	9×9	126	4×5	106
Example 2: S_1, S_2 and S_3 are assayed with A_1, A_2, A_3 and A_4	8×8×100	8×8	98	7×5	71
	7×7×120	7×9	112	4×5	83
	6×6×140	7×8	150	4×5	77
Example 3: S_1, S_2 and S_3 are assayed with A_1,A_2 and A_3	7×7×80	7×7	79	6×6	48
	6×6×100	6×8	93	5×5	58
	5×5×120	5×8	120	4×5	54

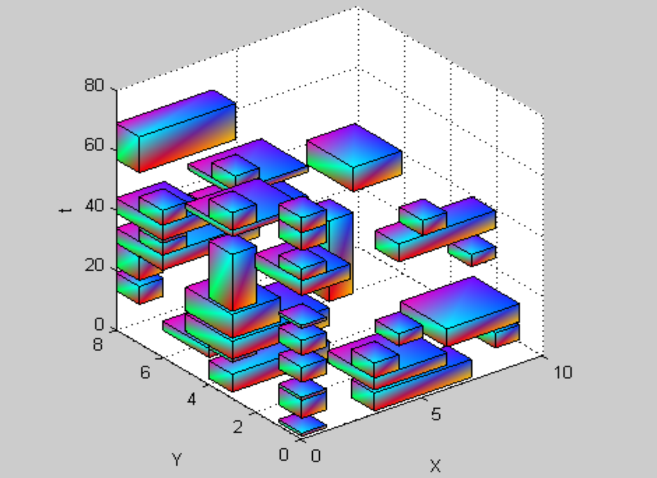

Figure 4. The 3D View of the Placement Result of the Example 1 with the 9×9×100 Design Specification

5. Conclusion

The placement of digital microfluidics-based biochips is a three dimensional packing optimization problem for multiple objectives. In this paper, a personification heuristic genetic algorithm based on the idea of three dimensional packing problems is formulated, of which the designing procedure and the CAD simulation are also provided. From the results, it can be found that the optimization of the completion time and biochip area achieved by the algorithm make the foundation of the studies on placement of defect-tolerant digital microfluidic biochips established, and in the meantime, the algorithm can also be used in many other three dimensional packing problem.

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