A MULTI-PIN DROPLET ROUTING ALGORITHM FOR DIGITAL MICROFLUIDIC BIOCHIPS

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Abstract: Digital microfluidic biochips have emerged as a major area of attention in the fields of Clinical Research, Medical diagnostics and are destined to revolutionize the biological laboratory procedure in coming years. As the use of Digital microfluidic biochips becomes widespread in safety critical biomedical applications – the need for enhanced automation for the complex biological procedures become more pronounced. In this paper, we attempted to design a high performance routing procedure applicable for multi-pin digital microfluidic biochips that deals with multiple source target routing in a concurrent manner using hierarchical approach. The avoidance of cross contamination is a key challenge in the design of a biochip. Our paper attempts to minimize this problem while parallel routing of droplets with an aim to optimize the cell utilization and minimize the overall routing time as well. The proposed method uses a special technique for clustering the sub-problems together and uses a hierarchical scheme to optimize the routing process. Empirical results obtained are quite encouraging.

1 INTRODUCTION

A biochip is a collection of miniaturized test sites (microarrays) arranged on a solid substrate that permits many tests to be performed at the same time in order to achieve higher throughput and speed.

The idea of low cost and reliable chip model that resembles an electronic chip that performs thousands of biological reactions within a very small area gained huge interest among scientists and biotechnologists in recent times. Because these chips can automate highly repetitive laboratory tasks by replacing cumbersome equipment with miniaturized, microfluidic assay chemistries, they are able to provide ultra-sensitive detection methodologies at significantly lower costs per assay than traditional methods—and in a significantly smaller amount of space.

One of the most advanced technologies to build a biochip is based on microfluidics where micro- or nano-liter droplets are controlled or manipulated to perform intended biochemical operations on a miniature lab, commonly known as a lab-on-a-chip (LOC).The major advantages of using microfluidics are i) Surface effects become prominent with high surface area to volume ratio, ii) Low thermal mass and high heat transfer, and iii) Low value of Reynolds number and thus laminar flows which only result in diffusional mixing.

The earlier generation of microfluidic biochips was based on continuous fluid flow in permanently etched microchannels using micropumps and microvalves for actuation. These devices relied on electrical methods such as electrokinetics to control the sample flows.

A major alternative is to manipulate liquid samples as discrete droplets. The second generation of microfluidic biochips is based on this approach and is referred to as Digital microfluidic biochips. Discrete droplets of the nanoliter volume are manipulated on a patterned array of electrodes. On a digital microfluidic biochip (*DMFB*), the electro-hydrodynamic force generated by the electrodes

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controls movements of the droplets. The electrodes in the microfluidic array are controlled by independent control pins, which actuate free movement of the droplets on the array. By assigning time-varying voltage values to turn on/off the electrodes on the digital microfluidic biochip, it is possible to move the droplets around the entire 2D array and perform fundamental microfluidic operations (such as, mixing reactions) for different bioassays. The applied voltages are changed according to the need for moving the droplets from one electrode to the other, and the process can be controlled by a processor of predefined clock frequency that determines the velocity of movement of the droplets (Su and Chakraborty, 2004). These operations performed under the control of the electrodes are reconfigurable operations because of their flexibility in area (electrodes involved) and in execution time. Digital microfluidic biochips allow continuous sampling and analysis capabilities for online and real-time chemical/biological sensing.

Digital microfluidic biochips have a vast multitude of applications including clinical diagnosis, environmental studies, and military operations. Due to their digital nature, any operation on droplets can be accomplished with a set of library operations like VLSI standard library, controlling a droplet by applying a sequence of preprogrammed electric signals (actuation sequences) (Zeng, Liu, Wue and Yue, 2007).Therefore, a hierarchical cell-based design methodology can be applied to a *DMFB*.

The first top down methodology for a *DMFB* proposed by (Su and Chakraborty, 2004) mainly consists of architecture level synthesis and geometry-level synthesis. The geometry-level synthesis in *DMFB*s broadly involves placement of modules (source, mixer and target) and droplet routing. During module placement, the location of each module is determined to minimize chip area or response time. In droplet routing, the path of each droplet transports it without any unexpected or accidental mixing under design requirements.

In this paper, attempts are made to route 2-pin and multi-pin nets (which imply number of droplet samples moving to the same target is greater than or equal to two) in digital microfluidic biochip using a hierarchical approach. The objectives are to optimize (i) the number of electrodes used to route all the droplets from source to target (via the mixer in case of multi-pin droplets) and (ii) the overall droplet routing time. This, in turn, optimizes the area, routabilty and throughput.

The organization of the remaining paper is arranged as follows. Section 2 deals with existing works on droplet routing. Section 3 depicts the fundamentals of droplet routing. Section 4 introduces the problem formulation with multi-pin droplet routing. Section 5 discusses the algorithm for clustering the sub-problems together to deal with maximum parallel routability. Section 6 describes the routing algorithm using hierarchical approach .Section 7 depicts the final results for the given test cases along with graphical representation of the clusters showing sub-problem connectivity. Finally, section 8 provides the conclusion with analysis of results.

2 EXISTING WORKS

A critical step in biochip automation is droplet routing, which provides an overall estimation of the net performance time as well as resource utilization. Numerous techniques are proposed for optimization of droplet routing in biochips. A graph coloring approach was proposed by (Akela, Griffith and Goldberg, 2006), which is applied to each successive cycle of direct addressing solution. In this work direct addressing was defined as the control mechanism of droplet movement over the electrodes by direct addressing of the micro-controller control unit. An acyclic graph was generated based on the movement time of the droplets and coloring was done based on concurrent routing of droplets. *DMFB* arrays with hardware limited row-column addressing are considered, and a polynomial-time algorithm for coordinating droplet movement under such hardware limitations was developed. Direct addressing method was also used by (Xu and Chakraborty, 2007) where the droplet routing problem is mapped into graph clique model. Droplet routing time is optimized by optimal partitioning of the clique model. (Lin, Yang, Wen, Ping and Sapnetkar, 2008) explored the use of direct addressing mode in their work of routing for biochip, using integer linear programming (*ILP*) to solve the problem. In works of (Hwang, Su and Chakraborty, 2006) dynamic reconfigurability of the microfluidic array is exploited during run-time. The proposed method starts with an initial placement technique. A series of 2-*D* placement configurations, in different time spans, is obtained in the module placement phase. Then appropriate routing paths are determined to complete droplet routing. The authors decompose a given problem into a series of sub-problems, based on their initial placement and solve them sequentially to find the ultimate solution. (Cho

and Pan, 2008) proposed a high performance droplet routing algorithm using a grid based representation. Their proposed algorithm initially checks which droplets can be routed freely (without any obstacle or blockage due to other droplets). Then the droplets are arranged to route in parallel without considering blockage. Routing of the remaining droplets is considered in presence of blockage and a concession zone was introduced to ascertain feasibility of the routing. Finally a compaction based algorithm was run to optimize the solution. In works of (Yang, Yuh and Chang, 2007) a network flow based method was proposed for droplet routing. The proposed method was based on non-intersecting bounding box technique. The bounding box of each net was first obtained. Then a set of nets having non-intersecting bounding boxes were chosen for routing. The remaining nets were routed using min-cost max-flow algorithm. An *A* search* algorithm was proposed by (Boahringer, 2006). The states of the source-target pairs at different times are differentiated using a graph representation. Then optimal path from source to target was chosen using the *A* search* algorithm. (Xu and Chakraborty, 2007) presented a droplet-routing-aware automated synthesis tool for microfluidic biochips. Droplet routability, defined as the ease with which droplet pathways can be determined, is first estimated and integrated in the synthesis flow. (Zhao and Chakraborty, 2009) proposed a droplet-routing method that avoids cross-contamination in the optimization of droplet flow paths. This approach targets disjoint droplet routes and minimizes the number of cells used for droplet routing. (Roy, Rahaman and Dasgupta, 2010) proposed a simple algorithm for concurrent path allocation to multiple droplets, based on the Soukup's routing algorithm proposed by (Soukup, 1978) together with the use of stalling, and possible detouring of droplets in cases of contentions. Selection of the droplets was based on the lengths of the respective source to target Manhattan paths. A partition-based algorithm for pin-constraint based design was proposed in (Xu and Chakraborty, 2006).

3 DROPLET ROUTING IN DMFBS

The primary objective of droplet routing was to transmit all the droplets from source to target within a 2D grid array while fulfilling all the necessary constraints. In this regard an efficient schedule has to be developed that provides an optimized routing both in terms of timing as well as electrodes utilization.

The droplets are sandwiched between two electrodes (Fig 1) and the motion is actuated from one electrode grid to another using the principle of Electrowetting on dielectrics. We model the droplet routing problem in *DMFB*s as a *2D-grid* (Fig 2). For each droplet, there exists a set of source grid locations, and a set of target grid locations. Each source to target combination is referred to as a net. If only one source and one target are involved in a given net, it is a 2-pin net. If multiple sources, mixers and a single target are involved, it is a multi-pin net. Two Sources, one Mixer and one Target combination is referred to as a 3-pin net (Fig 3). Our goal is to route every droplet, if feasible, from its source location to its target location possibly through mixers, subject to several constraints.

The constraints generally applied for droplet routing are defined as follows. For a successful droplet routing, a minimum spacing between droplets must be maintained to prevent accidental mixing. In cases of 3-pin nets or multi-pin nets, droplet merging is desired at specific locations termed as mixers. Several microfluidic modules required for mixing, splitting, storage and other operations are placed on the array. These are considered as obstacles in droplet routing.

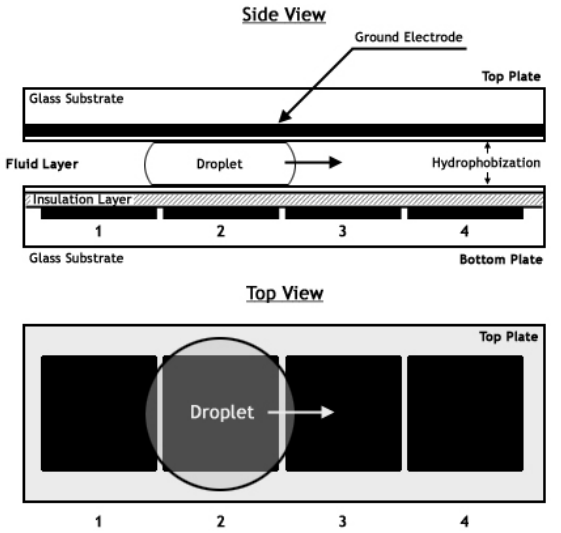

Figure 1: Droplet actuation principle in *DMFB* using *EWOD* (Hwang, Su and Chakraborty, 2006).

In order to avoid conflicts between droplet routes and assay operations, a segregation region is defined around the functional region of microfluidic modules. In this way, droplet routing can easily be isolated from active microfluidic modules. During

routing of multiple droplets concurrently in time-multiplexed manner, there are possibilities of intersection or overlapping of droplets coming in collision course. Certain fluidic constraints are introduced in order to avoid such undesirable behavior.

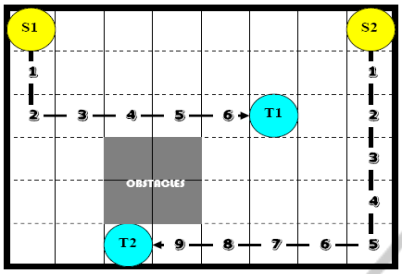

Figure 2: Droplet routing in a 2D Grid where S1, S2 represents. Sources; T1, T2 represent Targets along with timestamps and Obstacles (Latest arrival time = 10).

Let d_{id} at (x^t_i, y^t_i) and d_j at (x^t_j, y^t_j) denote two independent droplets at any given timestamp t. Then, the following constraints, generally called *Fluidic Constraint* should be satisfied for any time t during routing: (Roy, Rahaman and Dasgupta, 2010)

- Static constraint: $|x^t_i - x^t_j| > 1$ *or* $|y^t_i - y^t_j| > 1$
- Dynamic constraint: $|x^{t+1}_i - x^t_j| > 1$ *or* $|y^{t+1}_i - y^t_j| > 1$

Or $|x^t_i - x^{t+1}_j| > 1$ *or* $|y^t_i - y^{t+1}_j| > 1$

This implies that for any droplet at location (x,y)- all the locations (x+1,y),(x-1,y),(x,y+1),(x,y-1),(x+1,y+1),(x+1,y-1),(x-1,y-1),(x-1,y+1) are prohibited for any other droplet to enter at timestamp t and $t + 1$ in order to maintain the above mentioned fluidic constraints. Hence, all the locations neighboring (x,y) as referred to above comprise the *Critical Zone* (Fig. 4) for any droplet at (x,y) at time t.

The *Timing Constraint* provides the maximum allowed transportation time of a droplet in the given set.

4 PROBLEM FORMULATION

Parallel routing of droplets are necessary to optimize the latest arrival time. In most of the approaches described in Section 2, concurrent routing has been attempted for those droplets whose paths are free of obstacles. Then remaining droplets are taken care of for their routing to respective targets sequentially

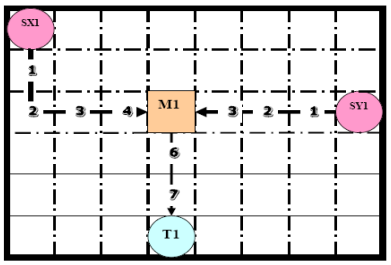

Figure 3: 3-Pin droplet routing with hierarchical approach with two sources SX1 and SY1, One Target T1; Latest arrival time (1st Generation – 5), Latest arrival Time (2nd Generation – 8).

using stalling and detour. In (Roy, Rahaman and Dasgupta, 2010) however an overall concurrent routing approach is adopted to obtain a virtual route plan depending on relative locations of modules, samples and targets. The results show encouraging improvements for both time and resource utilizations. However, no attempt has been made so far to address the issue for multi-pin droplets as only 2-pin cases were resolved in (Roy, Rahaman and Dasgupta, 2010) .Our work specifically attempts to resolve the issue of 2-pin and multi-pin droplets concurrently using a hierarchical approach for multi-pin droplets.

The routing problem can be formulated as follows: Given a two-dimensional array of electrodes placed over a square microfluidic biochip (a square layout area) as shown in Fig. 2 and Fig. 3. A set of module locations is given in a grid. A number of sub-problems clustered in different subsets provide the source, target locations for 2-pin nets and multiple source, mixer and corresponding target locations for multi-pin nets. The objective is to find the possible shortest path for each source to target (via mixer, if any) taking into consideration of the fluidic constraints mentioned in previous section and thereby route each droplet to its destination with optimum arrival time as well as minimal utilization of electrodes.

In the process, we have to cluster the sub-problems that comprise a total set into separate subsets to maximize the number of droplets in the individual subsets to be routed concurrently. The reason is that it is not possible to place all the sub-problems in a given test set at the same grid as it violates fluidic constraints for placement. Each cluster (subset of nets) is routed concurrently, whereas the different clusters are routed one after another in a sequence with clusters with largest number of samples being routed first and so on.

5 METHOD OF CLUSTERING OF SUB-PROBLEMS

Given a test case with *n* sub-problems. The fluidic constraints for placement of source target and mixers are as follows:

1. No two source location should coincide or be placed at critical zone (adjacent cell) of each other.
2. No Target location should coincide with other or with any other mixer or in any critical zone of mixer.
3. No Mixer should coincide with any other mixer, source, or target or in any critical zone of other mixer, source or target.

It is found that not all the sub-problems conform to the placement fluidic constraints. Hence, the aim is to cluster

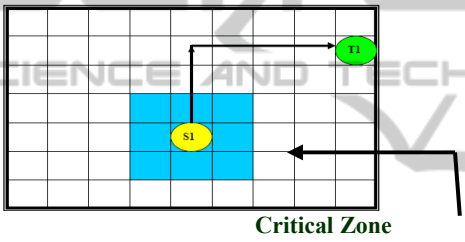

Figure 4: Critical zone around a droplet S1 in a moving state (Roy, Rahaman and Dasgupta, 2010).

maximum number of sub-problems in a subset together that do not violate the previously mentioned constraints and route them together. Then go for the next cluster, which contains next largest number of sub-problems, which are not already routed in the previous cluster. The process is continued until all sub-problems have been considered.

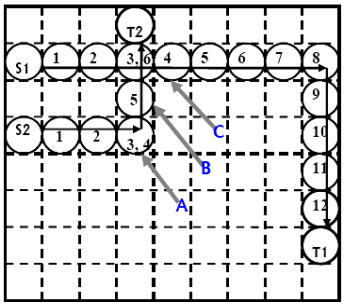

Figure 5: Example of droplet routing with time stall (Roy, Rahaman and Dasgupta, 2010).

5.1 The Clustering Algorithm

Input: A test case with *n* number of sub-problems, compatibility_list[i] for each sub-problem number *i*
initialized to null.
Step1: find the compatibility list for each sub-problem
for i = 1 to n
Add i to compatibility_list[i]
for j = 1 to n
check compatibily with i (if j ≠ i)
if compatible add j to compatibility_list[i]
end for
sort compatibility_list[i] in ascending order of
Sub-problem Number.
end for
Step 2: Find the final set of clusters
for i = 1 to n-1
for j = i+1 to n
find intersection of compatibility_list[i] and compatibility_list[j]
let number of elements in the intersection set be m
for k = 1 to m
if (k ≠ i) and (k≠ j)
check compatibility of k with other members
of the set from compatibility_list[k]
if any member is not compatible, exclude
them from the set comprising i, j and k
end for
end for
end for
finally x number of sets comprising all the numbers of
sub-problems are formed.
Step 3: Find out the set with largest number of sub-problems.
Step 4: Exclude these members from other sets.
Step 5: Check if all sub-problems are exhausted.
Step 6: If some sub-problems are yet to be routed repeat step 2 with remaining sets after the previously mentioned exclusion.

Compatibility of nets may be represented as a graph, with each node representing a net, and presence of an edge between a pair of nets indicating their compatibility (no violation of module placement constraints).

6 PROPOSED METHOD OF ROUTING FOR EACH CLUSTER

In this approach, we attempt an overall concurrent routing of the droplets grouped in individual clusters formed according the method stated in Section 5. The method is described below:

1. The overall time is measured in terms of timestamps for each source. For each source, the start time is initialized to zero and a timestamp increment of one is considered for each transition from one cell to its adjacent cell.

2. The Manhattan distance between each source, mixer, target combination is computed. For a 2-pin source $S_i(x,y)$ and Target $T_i(x,y)$ the distance D_i is computed as $[S_i(x) \sim T_i(x)]+ [S_i(y) \sim T_i(y)]$.For a 3-pin source $SX_i(x,y)$,$SY_i(x,y)$ and Mixer $M_i(x,y)$along with target $T_i(x,y)$ -- the distance D_i is computed as $[\{SX_i(x) \sim M_i(x)\}+ \{SX_i(y) \sim M_i(y)\}] + [\{SY_i(x) \sim M_i(x)\}+ \{SY_i(y) \sim M_i(y)\}]+ [\{M_i(x) \sim T_i(x)\}+ \{M_i(y) \sim T_i(y)\}]$. Same ordering of nets is used for multi-pin nets as well.

3. The Manhattan distance thus obtained for each droplet set is sorted in descending order. The routing of each droplet set (2- pin or 3-pin) is carried out in the same order.

4. Routing of the droplets is carried out using Soukup's routing algorithm. For 2-pin nets each source is routed directly towards the corresponding target. However, for 3-pin nets each source SX and SY is routed parallel to the corresponding mixer. This is termed as 1st Generation route. The largest arrival time T_{SM} among (SX → M) and (SY →M) is noted. Then the final mixed droplet from Mixer M is routed to Target T. This is termed as 2nd Generation route. In case of 2nd generation route, the timestamp starts from T_{SM} as determined earlier.

5. In case there is a clear path for any source to target or source to mixer or mixer to target route, then routing is completed easily. Detouring is required in the presence of obstacles.

6. Consider the case when droplet from a source arrives at a cell such that in the same timestamp droplet from another source is also reaching the same cell or in an adjacent cell within the critical zone. In such a case, any one of the two sources is stalled for a certain amount of time until the difference of timestamps between the two sources becomes at least two (Fig 5). The source with larger Manhattan distance among the two is allowed to route and the other one is stalled. However if it is found that there remains a scope of detour through a path which has been utilized before by some other droplet – if stalling takes too long (empirically if it is greater than 4 timestamps approximately) – detouring through utilized path is favorable – as it optimizes the utilization of resources in terms of electrodes.

7. Finally, one more possibility may be encountered while routing of droplets: deadlock. In this situation, a droplet S_x is stalled as it is in a collision course with another droplet S_y that has a higher routing preference due to larger Manhattan distance. However the second droplet S_y may also get stalled due to the movement of a Third droplet S_z which in turn can not move due to current position of S_x or S_y or any other blockage .In such cases it is necessary to identify the specific droplet which is responsible for deadlock – thereby detour it to a safe position(this phenomenon is known as retreat)through a different path and stall it to that safe position for a certain amount of time – which allows other two droplet to steer clear towards their respective destinations.

In this approach we resorted to route the droplets in an order of longest Manhattan distance first – the reason behind this is as follows: the one expected to take maximum time (approximately) is routed first without any chance of stalling, thereby the critical time, which tentatively defines the maximum arrival time remains unaffected. This technique provided encouraging improvement in Latest arrival time.

As already stated, during routing, attempt is made to have a trade off between stalling and detour. This is to optimize both time as well as total number of unit cells utilized for routing.

7 RESULTS

The two testbenches considered are *In_Vitro_1* and *In_Vitro_2*. *In_Vitro_1* contains twenty 2-pin droplets and six 3-pin Droplets with eleven sub-problems on a 16 x 16 grid. *In_Vitro_2* contains twenty-six 2-pin droplets and six 3-pin droplets with 15 sub-problems on a 14 x 14-grid electrode.

7.1 Results for In_Vitro_1

Number of Sub-problems = 11

Figure 6 represents a compatibility graph In vitro 1. Each node of the graph represents a sub-problem, and nodes of same color belong to the same cluster.

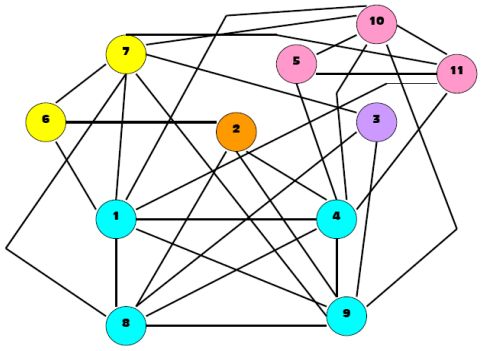

Figure 6: The sub-problem connectivity graph for In_Vitro_1 (based on compatibility with each other) Each color representing one cluster and each circle representing one sub-problem.

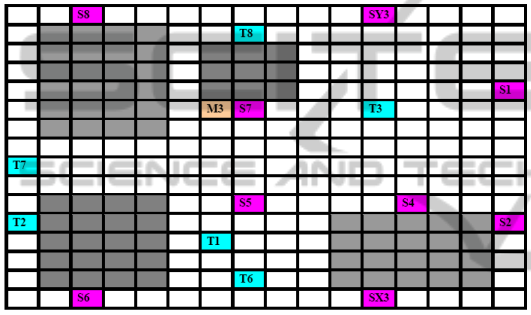

Figure 7: Sample placement diagram for Cluster 1 for In_vitro_1 (Source →Pink; Target →Blue, Mixer →Orange, Blockage →Gray).

Table 1a: Final set of clusters obtained for In Vitro_1.

Cluster Number	Set of sub-problems in cluster
1	{1,4,8,9}
2	{5,10,11}
3	{6,7}
4	{2}
5	{3}

Table 1b: Final Route table for all clusters for In_Vitro_1.

Grid	Cluster No{Set}	Number of droplets (2pin+3pin)	Latest Arrival Time	Electrode Utilization
16 X 16	1{1,4,8,9}	7+1 = 8	24	59
16 X 16	2{5,10,11}	2+2 = 4	21	51
16 X 16	3{6,7}	6+0 = 6	10	36
16 X 16	4{2}	2+1 = 3	26	47
16 X 16	5{3}	3+2 = 5	20	47
	Total - 5	**Total – 2-pin – 20 3-pin – 6**	**Total Time – 101**	**Net Electrode Utilization - 131**

7.2 Results for In_Vitro_2

Number of Sub-problems = 15

Table 2a: Final set of clusters obtained for In vitro_2.

Cluster Number	Set of sub-problems in cluster
1	{1,2,7,10,14,15}
2	{5,11,12}
3	{6,9,13}
4	{3}
5	{4}
6	{8}

Table 2b: Final Route table for all clusters for In_Vitro _2.

Grid	Cluster No {Set}	Number of droplets (2-pin + 3 - pin)	Latest Arrival Time	Electrode Utilization
14 X 14	1{1,2,7,10,14,15}	7+1 = 8	16	57
14 X 14	2{5,11,12}	6+1 = 7	15	37
14 X 14	3{6,9,13}	4+2 = 6	29	49
14 X 14	4{3}	4+1 = 5	23	50
14 X 14	5{4}	3+0 = 3	12	16
14 X 14	6{8}	5+1 = 6	16	37
	Total - 6	**Total – 2-pin – 26 3-pin – 6**	**Total Time – 111**	**Net Electrode Utilization - 95**

Table 3: A comparative result for total Electrode Utilization With other algorithms for two test sets – In_Vitro_1 and In_Vitro_2.

Test Design	Prioritized A* Boahringer (2006)	Two Stage Hwang, Su, Chakraborty (2006)	Network Flow Yang, Yuh, Chang (2007)	Cho Pan Algorithm Cho, Pan, (2008)	Our Algorithm
Name	Cell Utilization	Cell Utilization	Cell Utilization	Cell Utilization	Cell Utilization
In Vitro 1 (16 X 16)	269	263	237	258	131
In Vitro2 (14 X14)	failed	Failed	236	246	95

8 CONCLUSIONS

Here we have taken two specific test sets *In_Vitro_1* (having 20 2-pin droplets and 6 3-pin Droplets with 11 sub-problems on a 16 x 16 grid) and *In_Vitro_2* (having 26 2-pin droplets and 6 3-pin droplets with 15 sub-problems on a 14 x 14 grid). We attempted to cluster the sub-problems as shown in Table 1.a and table 2.a so as to handle as many sub-problems

concurrently as possible taking care of the fluidic constraints for placement (as stated in Section 5). The results of routing giving individual latest arrival time for each cluster as well as overall route time for each Test set is shown in Table 1.b and Table 2.b. The overall electrode utilization is also shown for each test case. A comparative study with other algorithms shows major improvement in terms of Cell Utilization for each test case as evident from the table 3.

Hence, in terms of resource utilization this algorithm shows remarkable improvement and is able to route maximum droplet as allowed by the placement constraints concurrently. This algorithm can be extended to more than three pins to be routed hierarchically. Also as the routing technique used here does not guarantee the shortest path, hence there remains further scope of improvement regarding this area, which may enhance the latest arrival time further.

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