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Research Note

Higher flexibility of reconfigurable digital micro/nano fluidic biochips using an FPGA-inspired architecture

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Abstract. Recent improvements in the bio-engineering area have composed wonderful opportunities to manipulate the bio-structures. Biochips are known as electronic platforms to decrease the experiment time and cost and improve the flexibility and automatability of operations. Digital micro/nano fluidic biochips can carry discrete droplets of experiment materials on the chip to perform the projected assays. In this paper, a new FPGA-inspired architecture is proposed for micro-fluidic biochips in order to improve the configurability and flexibility of the biochip and also reduce the number of controlling pins. The simulation results show that in the proposed architecture, number of controlling pins is improved by 6.35x compared with the direct addressing method and the total experiment time is reduced by 34% compared with the field-programmable pin-constrained method, improving configurability and flexibility.

1. Introduction

Biochip is an integrated fluidic and electronic device that provides necessary operations of biological assays, medical diagnostics, and chemical industries in an automatic and controllable manner. These chips are established on substrates made of glass, plastic, or silicon. Biochips are aimed for analyzing and manipulating of human or animal samples [1]. These chips are used in a wide range of medical research and commercial applications including forensic medicine, tissue grafting, medical tests, drug production, water and environmental experiments, new medicine discovery, genetic information extraction, drug and poison recognition, etc.

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The history of biochips started with genomic operations. These chips had the possibility of analyzing DNA fragments and genomic tests [2]. Then, protein arrays were manufactured with a technology similar to DNA arrays capable of determining amounts of special protein in biological samples [3].

Microfluidic biochips are categorized into continuous-flow and digital microfluidic biochips (DBFBs). The first category manipulates continuous flow of liquid through micro-channels, micro-pumps, and pressure sources [1]. The next category operates on the basis of controllable manipulation of discrete droplets of liquid on the surface of a two-dimensional array of electrodes enabling actuation of droplets through software-driven electronic control [1].

Digital microfluidic biochips can be used as point-of-care device (also referred to as lab-on-chip) in clinical diagnostics. For example, there is a biochip in [4] optimized with the protocol specific to detection of

malaria. Also, authors of [5] proposed a DMFB for performing Polymerase Chain Reaction (PCR). These types of chips have many advantages. However, they are application-specific; thus, they cannot be used for performing all types of assays.

Recent generations of DMFBs can be used as general-purpose chips for accomplishment of various types of bioassays. The general-purpose DMFBs utilize Printed Circuit Board (PCB) technology as the substrate for building two-dimensional arrays of electrodes. Electrodes can be controlled by some pins that must be addressed. Disadvantages of this architecture include design complexity and spatial and temporal assignment of modules [1].

It is predicted that microfluidic biochips are going to become a strategic technology for medical, military, and biological applications. But, current microfluidic biochips are faced with serious problems in flexibility and configurability. These weaknesses limit the chip providers to designing special-purpose biochips.

This paper proposes and evaluates a flexible and configurable general-purpose architecture. This architecture is induced for modern FPGAs and provides higher level of parallelism in bioassays.

The paper is organized as follows. Section 2 presents a review on biochips and their architectures are described in Section 3. The proposed architecture is illustrated in Section 4 and experimental results are presented in Section 5 and finally, the paper is concluded in Section 6.

2. A review on biochips

A biochip can perform thousands of biological activities, e.g. a computer chip which can perform millions of arithmetic functions in a second [6]. As mentioned before, modern biochips have been categorized in two groups: microarrays and microfluidic biochips. A microarray biochip consists of some tiny testable parts in a solid surface, each of which capable of conducting simultaneous experiments in order to increase utilization and speed [7]. On the other hand, a microfluidic biochip is composed of two distinct layers, microchannels and electronic substrate. The flow of the experimental materials can be controlled inside the micro-channels by the valves that are deposited in the substrate layer of the chip [7]. The main idea behind building microfluidic biochip is to combine all necessary functions for performing biochemical analysis on a chip through microfluidic technology. The microfluidic biochips are much more different and complicated than microarrays, providing various capabilities among which are containing evaluation, recognition, performing basic operations, and preparing samples. Two different generations of microfluidic biochips are described in the following subsections [7].

2.1. Continuous-flow microfluidic biochips

The first generation of microfluidic biochips were based on manipulating liquid flow via micro-channels fabricated onto the surface of the chip. The experimented fluid flows through the micro-channels on the surface of the chip under pressure of the external source, integrated mechanical micro-pumps, or electro-kinetic mechanisms. For instance, a common method in electro-kinetic method is electro-osmosis, which moves the liquid by an electrical field [8]. Figure 1 shows continuous-flow microfluidic biochip.

2.2. Digital microfluidic biochips

Digital microfluidic biochips (DMFB) are lab-on-chip devices for conducting large and complicated biochemical assays. These chips manage and hold micro- or nano-litter liquid and have high ability in biomedical recognition. Also, DMFBs can decrease the cost of bioassays and occupy small volume of lab equipment [9]. In a typical DMFB, droplet is replaced for closed channels in continuous-flow biochip. These biochips have open constructions and convert liquid to independent, separated, and controllable droplets and they can be manipulated for proper movement on the surface. Figure 2 shows a typical DMFB. The chip consists of a two-dimensional array of electrodes along with additional modules (such as I/O reservoirs, heaters, detectors, etc.) that can manipulate droplets of liquids. The liquid enters the chip from I/O reservoirs or by dispensing via special ports and then on-chip droplets can be manipulated by activating electrodes.

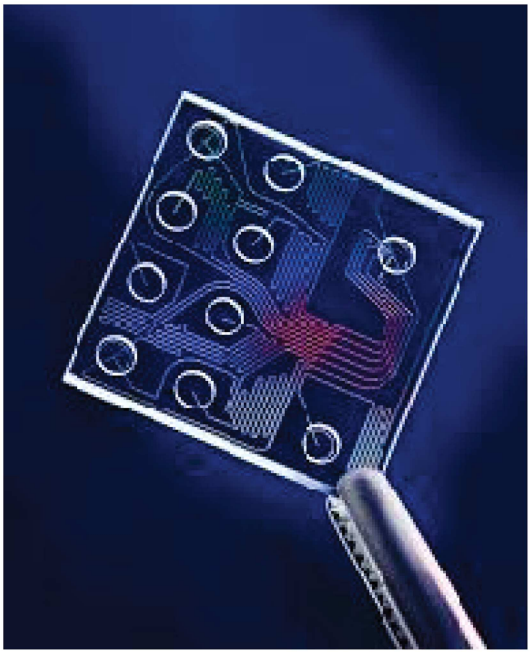

Figure 1. A sample of continuous-flow microfluidic biochip [6].

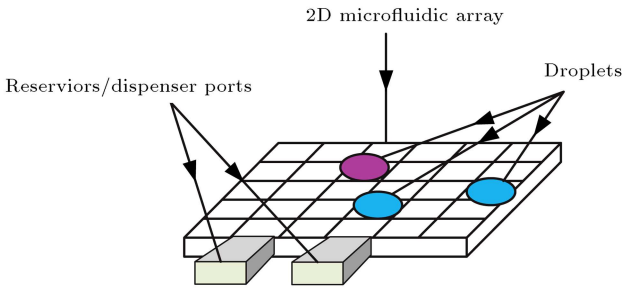

Figure 2. A sample of digital microfluidic biochip [6].

Manipulation of droplets on a DMFB is accomplished through Electro-Wetting on Dielectric (EWoD) mechanism. Digital microfluidic biochips are comprised of two parallel plates. The bottom plate contains an array of separated controllable electrodes whereas the top plate is covered by a continuous ground electrode. Droplets are sandwiched between the two plates; every droplet present onboard is held in its place as long as the electrode beneath the droplet is active [9].

As shown in Figure 3, each droplet has overlap with adjacent electrodes. When the electrode beneath the droplet is activated, an electrical field is created between conductive liquid droplet over the plate and the solid surface of electrode covered with dielectric. When the electrical field is applied to any neighboring electrode, while simultaneously deactivating the electrode beneath the droplet, the imbalance and surface tension cause the droplet to start moving towards the newly activated electrode [9,10].

Fundamental operations performed on a DMFB chip are as follows [11]:

- **I/O operation:** exchanging the liquid materials from/to source/sink;
- **Transport:** moving droplets on the biochip surface from/to main modules such as recognizer, converter, supplier, and so on (Figure 4(a));
- **Split:** splitting one droplet to smaller parts for parallel processing (Figure 4(b));
- **Merge/Mix:** mixing the droplets to create a new typical droplet (Figure 4(b) and (c)).

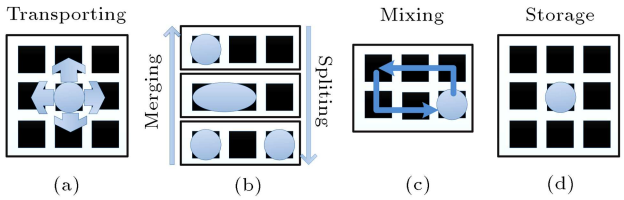

Figure 4. Basic operations in a digital microfluidic biochip [10,11].

3. Architectures of Digital Microfluidic Biochips (DMFBs)

Various architectures have been proposed for digital microfluidic biochips. These architectures are described in the following subsections.

3.1. Application-specific DMFB architectures

In application-specific digital microfluidic biochips, type, number, and location of modules and traveling paths of droplets are fixed at design time for some specific application (bioassay). The important aspect in this type of architectures is that a special chip should be designed for each assay which is not affordable and reasonable for the price [1].

An application-specific biochip for recognition of malaria is shown in Figure 5. The biochip executes some special operations such as infected cells separation, DNA extraction, DNA proliferation with PCR, and optic recognition with SPR. As shown in Figure 5, the biochip is designed and fabricated for a specific application and cannot be reprogrammed for other applications. The chip contains 13 reservoirs, mixing and detection areas, and a bus of electrodes for transporting the droplets between different areas of the biochip during the bioassay execution [1].

3.2. General-purpose DMFB architectures

In general-purpose DMFB architectures, place attribution should be determined at design time, but time attribution should be decided at the usage time. In other words, the location of modules should be fixed at design time and solely the scheduling management should be performed at the usage time. As can be seen in Figure 6, allocation of droplet routing paths between modules (dark columns and rows) has been

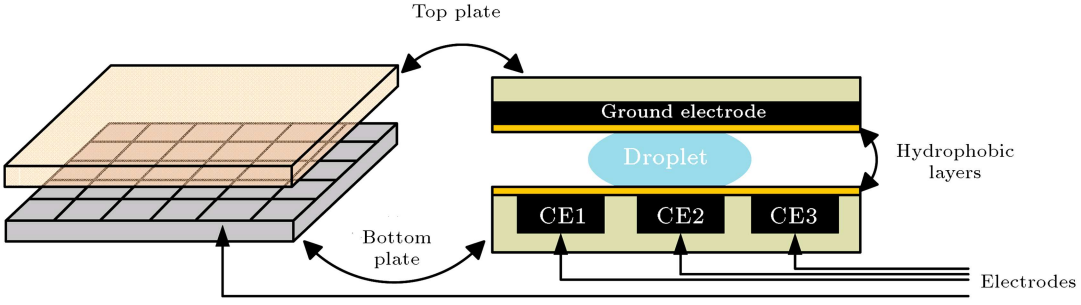

Figure 3. Basic cell in digital microfluidic biochip [9,10].

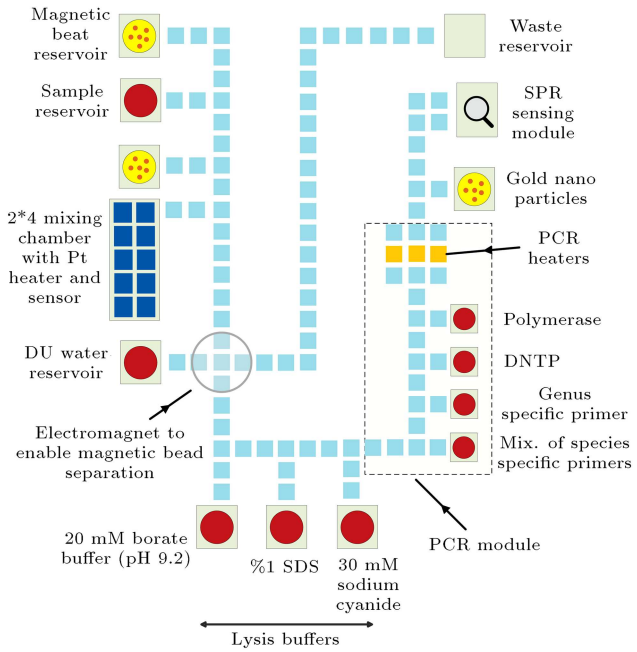

Figure 5. An example of application-specific digital biochip for recognition of Malaria [4].

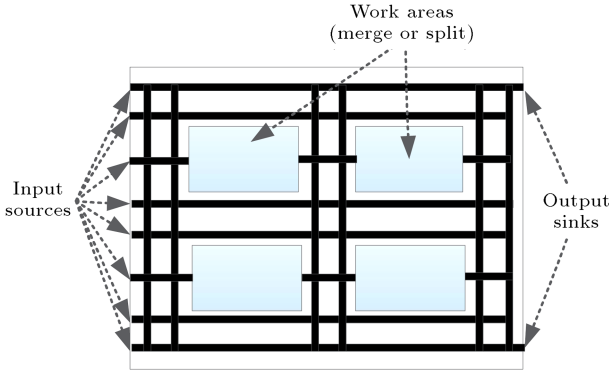

Figure 6. General-purpose DMFB architecture [12].

accomplished at design time; thereby, it cannot be changed during the rest of DMFB lifetime [12]. The light areas show working parts where only splitting and mixing operations can be performed. With the particular architecture shown in 6, only splitting and mixing operations can be done in parallel, then the resulting droplets should be sent to external sources. Considerable amount of time should be spent to send out results of splitting and mixing operations because external sources (such as detector) are located around the chip [12].

3.3. Reconfigurable DMFB architectures

In reconfigurable DMFB architectures, place and time attributions are determined at the usage time. Position of detector modules and I/O ports should be determined and fixed at the design time, but the attributions of other types of modules (mix, store, and merge) should be resolved after the design time. Figure 7 shows a reconfigurable architecture where the entire area of chip is covered with electrodes, each of which should be controlled by a pin. In the figure, the electrodes, input/output ports, and detector modules are shown. The main operations can be performed on any electrode in the two-dimensional array of electrodes. For example, some groups of electrodes can be operated as a mixing module during one period of time and during another time slot, the same groups of electrodes might operate as a splitting module [13].

Figure 8 shows the synthesis flow of a DMFB bioassay. Every bioassay is represented in the form of a Directed Acyclic Graph (DAG). Within the DAG, each node represents a microfluidic operation (such as dispensing, output, splitting, detecting, and mix-

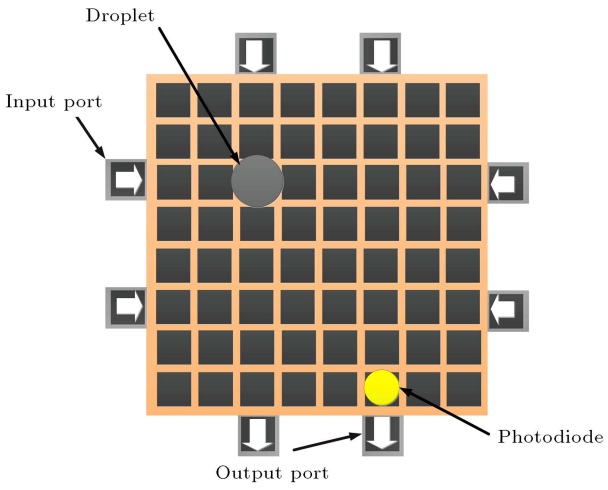

Figure 7. Top view of a reconfigurable architecture [13].

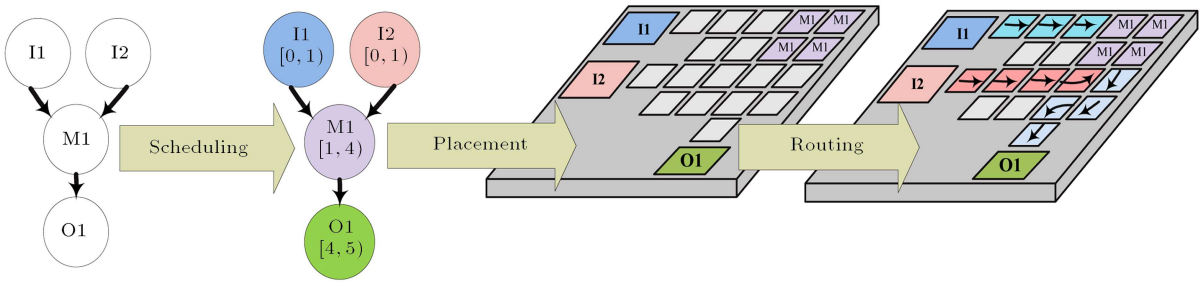

Figure 8. Synthesis of a DMFB [12].

ing) and each edge shows dependencies and priorities between microfluidic operations. The scheduling of operations in a DAG should be performed to determine the starting and ending time steps of each operation, consequently, the location of performing every scheduled microfluidic operation is decided during the placement stage and the droplet routing paths between the operations will be realized.

For next steps, pin assignment is done to control the moving of droplet from one electrode to other one based on the scheduled DAG. Pin assignment can be done with direct-addressing or pin-constrained method [10]. In direct-addressing method, each controlling pin is allocated to one electrode and in pin-constrained method, each controlling pin can control some electrodes.

3.4. Field-Programmable Pin-Constrained (FPPC) DMFB architectures

As mentioned in the previous section, using separate pins for controlling of each electrode can increase flexibility of the DMFB. But this architecture is infeasible for real large chips due to the wire-routing complexity along with the number of PCB layers which would considerably increase the manufacturing cost of the DMFB. In [10], a general-purpose architecture is presented in order to decrease the number of controlling pins and the corresponding costs. In this method, positions of modules are fixed and various vertical and horizontal droplet routing paths are allocated. In other words, time scheduling is performed at the design time while the placement is determined at the usage time. Considerable areas of the chip surface are unusable that are used for the separation of modules. Moreover, I/O reservoirs can be located anywhere on the periphery of the chip. The two aforesaid problems can be addressed for this architecture; the former is that larger chips are needed for large assays, and the latter is that synchronizing the mixing operation may be faulty since all the mixing units work simultaneously. The proposed architecture in [10] is shown in Figure 9.

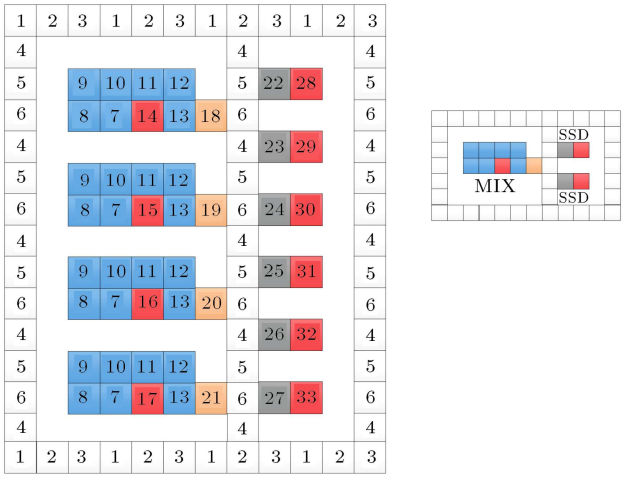

Figure 9. The field-programmable pin-constrained DMFB [10].

4. The proposed DMFB architecture

In the previous section, four types of DMFB architectures were described. The special-purpose biochips can be designed and implemented for a special type of applications, but they are limited to the target application, thus lacking reconfigurability and programmability. The mentioned general-purpose biochips can be used for limited types of assays with very low flexibility. The third type of DMFBs has been proposed to improve the flexibility of microfluidic operations. They uniform two-dimensional arrays of controllable electrodes that can be configured to perform bioassays. Since each electrode is controlled via an external pin, significant wiring complexity and costly multi-layer Printed Circuit Boards (PCBs) are incurred for architectures appropriate to large bioassays. In the Field-Programmable Pin-Constrained (FPPC) DMFBs, the wiring complexity is reduced while at the same time the flexibility is also reduced. The FPPC DMFBs use a routing column among the modules (SSD, MIX, etc.) as a result of reduction in flexibility. With all the previously reviewed architectures, the parallelism of bioassay operations, especially for large bioassays, has not been considered.

In this section, a new architecture for digital microfluidic biochips is presented, which is inspired from the conventional FPGA devices to maintain a reasonable trade-off between efficiency and flexibility. The proposed architecture can be reconfigured for

various bioassays or biochemical evaluations without new fabrication of the chip. The main contribution of this architecture is increased flexibility and parallelism of the biochip while maintaining a reasonable trade-off between efficiency and flexibility. In the proposed architecture, instead of Configurable Logic Block (CLB) in the FPGA context, Configurable Bio-Cell (CBC) is used. Each CBC contains the primary modules necessary for performing biochemical and laboratory procedures. The input and output ports of the experiment material are same as the FPGA I/O ports. In other words, the proposed biochip is a two-dimensional array of CBCs. The electrodes are used to control the droplet routing paths between the CBCs. The architecture is called Programmable Bio-Cell Matrix (PBCM). Each CBC contains the required modules for basic operations in DMFB which can perform any operation. Figure 10 shows the structure of a CBC that contains the following modules:

- A mixing module which is assigned to pins 7 to 14;
- Input-output port of the mixing module or mixer I/O that is assigned to pin 15;
- Two Split-Store-Detection (SSD) modules which are assigned to pins 18 and 19;
- Input-output ports of SSD modules or SSD I/O which are assigned with pins 16 and 17;
- Droplet routing-path electrodes which are assigned with pins 1 to 6.

In Figure 10, the electrodes numbered 1-3 within each cell are used to transfer droplets in horizontal buses whereas the electrodes numbered 4-6 are used to transfer droplets in vertical buses. These electrodes should be indexed similarly in all the CBCs so that all electrodes of the CBCs with the same index are connected to one controlling pin and activated simultaneously. The electrodes 7-13 form the mixing modules where the mixing operations take place.

The electrodes 7-13 are common within all the cells and get activated at the same time, but electrode 14 is used to store the mixed droplet in each cell and is controlled with an individual pin within each cell. Electrode 15 is the input-output port of the mixing modules, which is used to enter or exit droplets and should be assigned with an individual pin within each cell. This ability is crucial so that one droplet in a cell can exit the mixing module, while other droplets remain in their corresponding cells for some arbitrary additional time steps. The electrodes numbered 15-19 are used for storing, splitting, and detecting microfluidic operations and are controlled with individual pins within different modules. During execution of bioassays, droplets need to be detected by external sources; these detectors should be located above SSD electrodes and perform detection operation within some time steps. Connections between SSD modules and droplet routing paths are established through electrodes assigned with individual pin numbers 16-17.

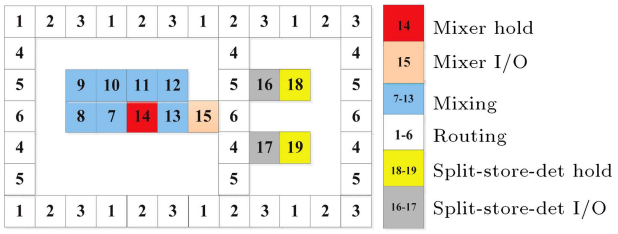

Figure 10. The structure of a Configurable Bio-Cell (CBC).

In Figure 11, a PBCM with 9 cells is shown whose CBCs have a similar structure to that in Figure 10, in which all the CBCs are connected together using the droplet routing paths. Input/output sources and dispensers are located around the chip. Given the abovementioned explanations, the biochip in Figure 11 can perform 9 parallel mixing, splitting, and storage operations on a minimum of 18 droplets. The architecture is useful for large bioassays with lots of simultaneous operations thus obtaining shortened bioassay execution times through parallelism of microfluidic operations. On the other hand, the extra cells can be deactivated to reduce power consumption for small bioassays that do not need all those cells.

5. Experimental results

The proposed DMFB architecture is implemented in UCR SSS framework [14-16] on a 2.26 GHz Intel Core 2 Duo Processor P8400 CPU and 3GB of RAM in order to evaluate efficiency of the architecture. It is worth to note that the UCR SSS is a widely used and open source DMFB synthesis framework to implement

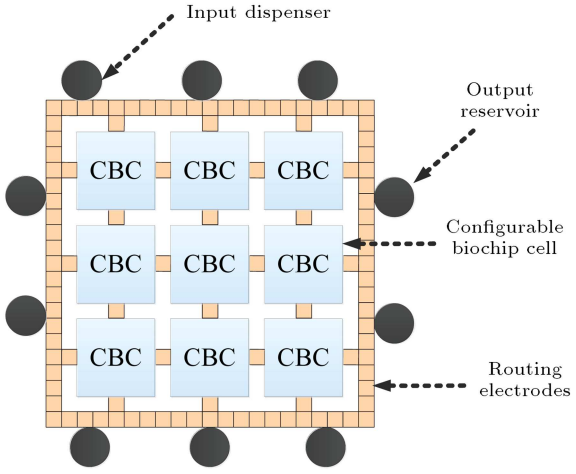

Figure 11. A schematic view of a PBCM with 9 CBCs.

Table 1. The simulation results comparing the proposed design with [12] and [10] based on the number of electrodes and pins.

Benchmarks	Array dim.			# Electrodes used			# Pins		
	DA	FP	PBCM	DA	FP	PBCM	DA	FP	PBCM
PCR	15*19	12*21	42*27	285	153	178	285	43	35
In-vitro 1	15*19	12*21	42*27	285	153	178	285	43	35
In-vitro 2	15*19	12*21	42*27	285	153	178	285	43	35
In-vitro 3	15*19	12*21	42*27	285	153	178	285	43	35
In-vitro 4	15*19	12*21	42*27	285	153	178	285	43	35
In-vitro 5	15*19	12*21	42*27	285	153	178	285	43	35
Protein split 1	15*19	12*21	42*27	285	153	314	285	43	57
Protein split 2	15*19	12*21	42*27	285	153	314	285	43	57
Protein split 3	15*19	12*21	42*27	285	153	314	285	43	57
Protein split 4	15*19	12*21	42*27	285	153	314	285	43	57
Protein split 5	15*19	12*25	42*27	285	177	314	285	49	57
Protein split 6	15*25	12*29	42*27	375	203	314	375	55	57
Average				**292.5**	**157.2**	**246**	**292.5**	**44.5**	**46**
Improve vs. FP									**-3%**
Improve vs. DA									**6.35x**

and evaluate the CAD algorithms of digital microfluidic biochips. It has a common interface and flexible internal data structures that can be updated for any new technology [16]. The proposed architecture is evaluated in terms of number of electrodes, number of controlling pins, and the total bioassay execution times. A 3*3 CBC structure is used as the architecture for execution of bioassays. The proposed architecture is compared with the presented DMFB design in [12], which is based on direct-addressing of electrodes with an individual controlling pin per electrode and also with the Field-programmable Pin-constrained (FP) design in [10]. The simulation results of the proposed architecture in this paper are represented with PBCM.

Table 1 compares the simulation results of the proposed architecture (PBCM) with existing architectures (DA and FP). In this table, the column of array dimension shows the number of rows and columns in the biochip. The columns of # Electrodes and # Pins represent the number of electrodes and number of pins, respectively.

It is worth noting that the main benefit of the proposed architecture is its programmability that provides high level of flexibility. As can be seen in Table 1, the number of controlling pins in the proposed architecture is improved by 6.35x compared with the DA method and is only 3% worse than that in FP. Both DA and FP are special-purpose architectures that can only be used for speciffic assays.

Table 2. Comparing results of the suggested method with those of [10] in terms of total experiment time.

Benchmark	# Time steps	
	FP	PBCM
PCR	1087	985
In-vitro 1	1459	1050
In-vitro 2	1982	1152
In-vitro 3	2123	1260
In-vitro 5	2221	1388
Average	1774	1167
Improvement to FP		**34%**

Moreover, Table 1 shows that the number of electrodes in PBCM is significantly more than that in FP method and less than that in DA method. Higher number of electrodes allows for increased functionality and flexibility. Results of Table 1 represent that the proposed architecture provides better functionality and higher flexibility along with less number of controlling pins (in average). Increasing the number of electrodes may change the area and cost of DMFB in small quantities. Therefore, extra electrodes cause negligible overhead in terms of PCB layers and cost.

Table 2 shows the experimental results in terms of total execution time of bioassays. In this table, the column of # Time Steps shows the total number of time

steps required for completing each bioassay. Time step is the time unit required for movement of one droplet from one electrode to another one.

Considering the results presented in Table 2 and given the fact that the same scheduling and placement algorithms have been used, the total number of time steps consumed for the suggested method is about 34% lower than that for the FP method in average. The improvement is due to the parallelism of the main microfluidic operations. In the suggested method, merging, splitting, and detecting operations are done separately in distinct modules and blocks but all of them are performed in parallel with the same pin. In a bioassay, droplets are transferred to a CBC block and saved in SSD modules of the CBC block after the operations. The droplets are kept in the CBC blocks and moved to other CBC blocks to merge with other droplets or split into new droplets. Therefore, many of the droplets can be processed in parallel with other droplets.

As this happens, the time of executing bioassays, especially huge bioassays, will decrease because many of mixing and detecting operations are performed separately and in parallel. On the other hand, the suggested biochip can run any bioassay, especially bioassays with large number of mix operations, on one chip and there is no necessity to increase the dimension of chip for larger bioassays. Moreover, the proposed architecture method can reduce power consumption because unused electrodes or CBC blocks can be turned off in case of small bioassays.

6. Conclusion

In this paper, a new FPGA-inspired architecture was suggested for digital microfluidic biochips. The architecture could be configured for any bio-chemical treatment with very high degree of flexibility. Moreover, the architecture provides the potential of huge parallel operations.

The experimental results showed that the proposed architecture reduced the total time steps by about 34%, while the number of controlling pins was reduced 6.35x compared with the direct-addressing method. It is worth noting that results would be better for larger boiassays that can be parallelized massively.

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