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"Optimization of Droplet Routing in Digital Microfluidic Biochips using the Concurrent Manhattan Routing with Stalling and Detouring (CMRSD) Algorithm"

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Abstract: The Concurrent Manhattan Routing with Stalling and Detouring (CMRSD) algorithm revolutionizes existing routing methodologies in Digital Microfluidic Biochips (DMFBs) by introducing innovative features to enhance efficiency and robustness. This algorithm initiates concurrent routing, enabling simultaneous droplet movement, and thereby reducing completion time. Stalling mechanisms resolve conflicts effectively by temporarily halting droplet movement, while prioritization based on Longest Manhattan Distance optimizes routing by tackling challenging routes first. Moreover, detouring strategies provide flexibility in route planning, ensuring adaptability to dynamic conditions. Through extensive experimentation and analysis, the CMRSD algorithm demonstrates remarkable performance in minimizing contaminations, optimizing route lengths, and streamlining droplet transportation in diverse scenarios.

Keywords: DMFB, CMRSD, Electrowetting-on-dielectric, Manhattan Distance, Hadlock's routing

Introduction

Recent years have seen a rise in the use of biochips based on microfluidics for the processing of biochemical data. These tiny microfluidics-based biochips are capable of enzymatic analysis (including lactate, glucose, and pyruvate assays of human physiological fluids like saliva, urine, etc.), large parallel drug discovery, and drug monitoring [1]. These biochips, sometimes known as "labs on a chip," simplify once labor-intensive laboratory processes by replacing cumbersome laboratory equipment with a composite micro-system. These biochips outperform more cumbersome and expensive technologies due to their compact size, high sensitivity, and low cost. They enable the control of micro- or nano-liters of fluids, cutting down on sample size, reagents volume, and energy requirements [2]. There are two methods for regulating fluid flow in microfluidic biochips. One is the use of micro-pumps, micro-valves, and micro-channels to ensure a constant flow of fluid. The other method involves manipulating liquids in the form of individual droplets and is just as efficient. The droplet based technique is known as digital microfluidics [3]. The microfluidic array cells are all identical in design, however with this method, individual droplets are controlled. The technique outperforms continuous flow systems because of its dynamic reconfigurability. During the course of a bioassay, a population of cells may go through a period of dynamic reconfiguration that modifies their functional behaviour [4].

According to the International Technology Roadmap for Semiconductors 2007 [5], the development of effective, affordable devices for the bio-medical domain is anticipated to emerge as a field tied to embedded systems in the near future. These gadgets, known as biochips (sometimes referred to as lab-on-chips), were developed in the late 1980s and are closely related to developments in genomics. Advances in the analysis and amplification of deoxyribonucleic acid (DNA) fragments led to the development of DNA microarrays, a type of genetic testing utilizing two-dimensional arrays of biosensors. On such devices, photolithography or ink-jet printing is used to attach thousands of biosensors (DNA fragments) to a substrate (often glass or silicon), and the hybridization process between those biosensors and fragments of target

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DNA is studied. Numerous uses for DNA microarrays exist, such as drug development, genotyping, mutation analysis, and disease diagnosis [6]. The first protein arrays were created in the late 1990s as a result of developments in genomics and a growing interest in biological systems.

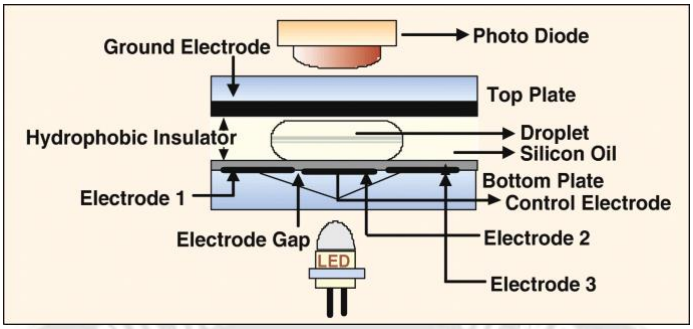

Figure 1: Digital Microfluidic Biochips

Similar to the way DNA arrays are created, thousands of proteins serve as the substrate in the creation of these devices, which are then exposed to various chemicals. As a result, clinical diagnostics and drug discovery can now utilize protein concentration measurements in biological samples (such blood) for their respective purposes [7]. In order to reduce the size of laboratories, scientists have developed microfluidic biochips, which can perform biochemical reactions in liquid. Microfluidic devices may be able to perform all of these activities on a single chip [6], whereas traditional biochemical analysis labs need large amounts of fluid (milliliters or liters). Microfluidic biochips come in two different flavors. Figure 1 illustrates an instance of the initial category, wherein a fluid in constant motion is regulated through the utilization of an external pressure source or a mechanical micro-pump that is integrated within the system. The complexity of biological processes necessitated the development of microfluidics for large-scale integration, which has been made possible by recent developments in soft lithography production techniques. This method integrates hundreds to thousands of micro-mechanical valves and control components on the chip, allowing for the simultaneous execution of many more experiments [8].

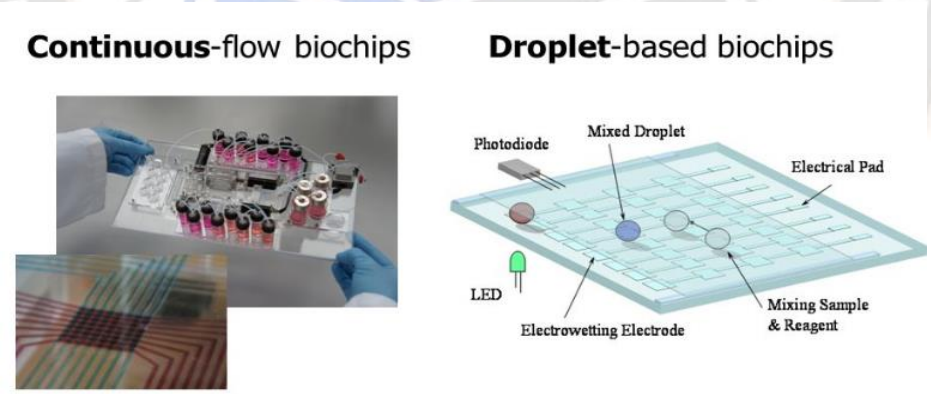

Figure 2: Routing-Based Synthesis of Digital Microfluidic Biochips

Biochips are miniature electronic circuits that are engineered to execute a precise form of biological analysis. The utilization of microfluidics technology enables their realization. Integrated functionality encompasses various processes such as detection, pre-treatment, and sample processing in microfluidic assays. There are two types of microfluidic biochips available, namely continuous flow and droplet based [9].

Compared to traditional closed-channel continuous-flow systems, innovative open structures offer notable benefits by separating the liquid into individual programmable droplets that can be controlled to move across a substrate [10]. The existing body of literature presents a diverse array of approaches aimed at effectively controlling microfluidic droplets. The Electrowetting-on-dielectric (EWOD) technique has garnered significant attention in contemporary times. The present study centers on biochips utilizing electrowetting-on-dielectric (EWOD) technology, commonly referred to as digital microfluidic biochips [11].

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The fundamental unit of an EWOD-based biochip consists of a pair of glass plates arranged in parallel, as depicted in Figure 2. The lower plate exhibits a prescribed arrangement of electrodes, while the upper plate features an uninterrupted ground electrode. The electrodes utilized in the study are composed of indium tin oxide (ITO), a material that exhibits optical transparency. In order to enhance the capacitance between the droplet and the control electrode, and reduce surface wettability, a hydrophobic Teflon AF dielectric insulator is utilized on both the top and bottom plates. Pollack's [2001] work provides a detailed and thorough explanation of the production process. The experimental setup involves the placement of droplets containing biological samples between two plates, with an intermediary filler medium, such as silicone oil, separating them. According to Fair et al. (2004), the utilization of silicone oil as a filler medium enables the reusability of microfluidic biochips. In order to induce directional movement of a droplet, an adjacent electrode is subjected to a control voltage while the electrode situated directly beneath the droplet is deactivated. The accumulation of charge at the interface of the electrode and insulator, resulting from the electrowetting on dielectric (EWOD) phenomenon, induces the formation of a gradient in surface tension within the interstitial region separating the electrodes. This gradient propels the droplet in a forward direction. According to Pollack (2001), the manipulation of the electrical potential across a series of electrodes, referred to as electrowetting, has the potential to facilitate the linear movement of liquid droplets with a volume of nanoliters. According to Pollack et al. (2002), it is possible to regulate the velocity of droplets within a range of 0 to 90 V, which enables the droplets to attain a maximum speed of 20 cm/s. The illustration presented in Figure depicts a planar arrangement of electrodes that can be employed for the purpose of conveying droplets in patterns specified by the user. This can be achieved by exerting voltage control in a clocked manner, without necessitating the use of micropumps or microvalves. The utilization of a standardized and adjustable configuration facilitates the implementation of a structured and compartmentalized methodology in the development of microfluidic biochips. It is hypothesized that a multitude of thoroughly characterized cells can be utilized in the development of a digital microfluidic biochip on a large scale, similar to the construction of advanced VLSI circuits through the use of well-characterized transistors.

Methodology

The Concurrent Manhattan Routing with Stalling and Detouring (CMRSD) algorithm addresses the limitations of existing routing methods by introducing several key features. Concurrent routing initialization enables simultaneous droplet movement to enhance efficiency and reduce completion time. Stalling mechanisms resolve conflicts by temporarily halting droplet movement, while prioritization based on Longest Manhattan Distance optimizes routing by addressing challenging routes first. Detouring strategies allow for flexible route planning, ensuring robustness in dynamic conditions.

Droplet formed

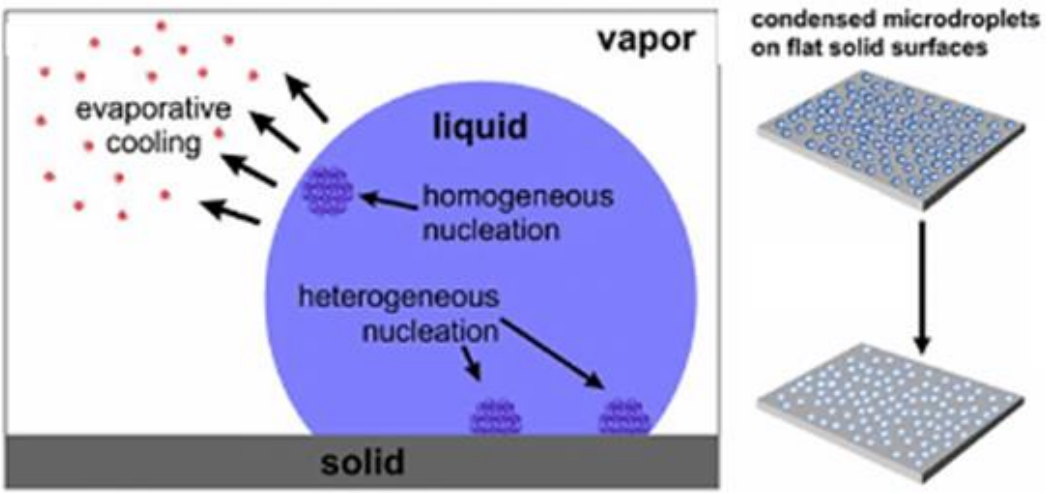

Figure 3: Homogeneous and Heterogeneous nucleation occur

Figure 3 illustrates the various ways in which water droplets can freeze, namely homogeneous and heterogeneous freezing. In homogeneous freezing, the process occurs uniformly within the droplet itself, while heterogeneous

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freezing involves the presence of external surfaces or particles triggering the freezing process.

Environmental factors, such as evaporation and the presence of contaminants, can influence homogeneous ice nucleation. Researchers have attempted to calculate the rates of homogeneous ice nucleation using coarse-grained models, considering factors like evaporation.

On flat, solid surfaces, the rate of ice nucleation was observed to be significantly higher for hydrophobic surfaces compared to other surfaces. This finding was established through experiments conducted in closed cells, where the effects of evaporation and condensation were taken into account.

Problem Formulation

In the context of a 2D square layout of a Digital Microfluidic Biochip (DMFB) with dimensions n x n, the configuration includes preplaced two-pin and three-pin nets, denoted by x and y, respectively. These nets are further consolidated into a total number of two-pin nets, represented as m = x + 3y. Each of these two-pin nets corresponds to a routing zone within the DMFB.

The primary objective is to estimate the total number of route paths (m) while ensuring optimal deviation to minimize the number of crossovers. Additionally, the goal is to achieve the shortest possible path length for each net.

To elaborate, the m routing zones, each associated with a two-pin net, need to be strategically planned to minimize crossovers. Crossovers in this context refer to points where the paths of different nets intersect, which can lead to interference and affect the functionality of the biochip.

Achieving optimal deviation involves planning the route paths in a way that minimizes the chances of crossovers occurring. This can be accomplished through careful design and allocation of routing zones. The goal is to find a balance between the shortest path length for each net and the overall reduction in crossovers.

Considering the square layout of the DMFB, the design process should take into account the specific characteristics of the biochip to create an efficient routing strategy. This may involve algorithms and optimization techniques to determine the optimal paths for the two-pin nets, considering the constraints imposed by the three-pin nets.

Efficient Route Allocation for Two-Pin Nets in Square DMFBs

In the problem formulation, we begin with m two-pin nets, each assigned a route zone. The route zones of three-pin nets, formed by the intersection of the route zones of two-pin nets, are excluded. The problem involves s intersection regions among these route zones, and a route zone graph GRZ (D, E) is created, where each node represents a route zone, and each edge represents a zone intersection.

Each edge in GRZ is assigned a weight (w), indicating the number of cells constituting the corresponding intersection. A Manhattan path is plotted from source to target for each net i. When these paths encounter microfluidic modules or hard blockages, deviations are initiated using Hadlock's routing method to reach the target. These paths tentatively ensure the shortest possible routes with minimal deviations.

The lengths of the route paths for each net are computed, and a table for GRZ is defined, listing each node with columns for node degree, computed path length, and total edge weight associated with overall intersections for each net.

Nets with the maximum node degree are identified, and those with the highest degree are given higher deviation preference. If multiple nets have the same degree, preference is given to the one with lower intersection area coverage, represented by total edge weight. If degrees and edge weights are also the same, preference is given to the net with a shorter path length.

Based on these preferences, the route path for the net with the highest deviation preference is plotted to minimize possible deviations. The process aims to reduce the number of contaminations, likely by optimizing the routing of nets through the defined route zones and minimizing deviations around obstacles.

Algorithm (main_algorithm):

Initialize variables m, nets with preplaced nets.

Resolve all nets into 2-pin paths.

Sort nets in descending order of distances.

Handle passage through hard blockages and update paths.

Process transportation with contamination avoidance:

Select 2-pin nets as route zones.

Form route zone graph and calculate weights.

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Form a path intersection graph and assign preferences.

Sort nets in ascending order of preference and perform deviation.

Store all paths after completion of deviation.

Simulation Tool

The DMFB Static Simulator serves as a crucial tool for assessing the effectiveness of a particular approach within the domain of Digital Microfluidic Biochips (DMFB). This software, built using C++, offers an open-source platform for researchers to simulate and analyze various strategies and algorithms.

Utilizing the capabilities of an Intel(R) Core i7 processor running at 3.40 GHz and supported by 4 GB of RAM, the simulation process is conducted efficiently, allowing for complex computations and analyses to be performed within a reasonable timeframe.

Analysis

The 16 x 16 layout of a 2D Digital Microfluidic Biochip (DMFB) employs six droplets organized across four microfluidic modules to execute various biochemical assays efficiently. This configuration creates six routing zones, facilitating droplet movements for simultaneous task execution.

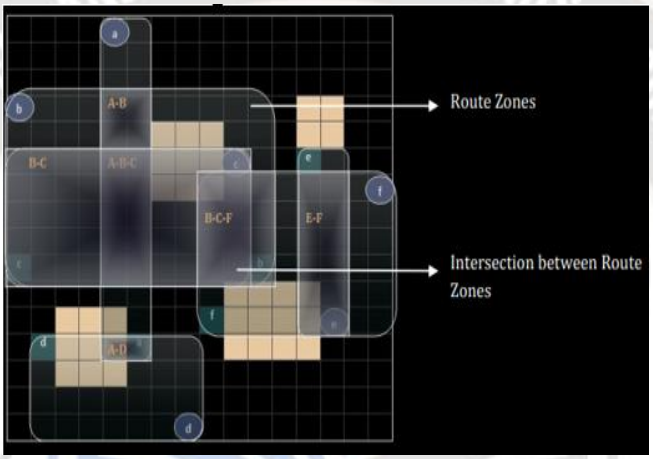

Figure 4: Tracing Paths at Intersections

Graphical representations such as Figure 4 and Table 1 illustrate intersection points between route zones, aiding in understanding spatial connections within the transportation network. Strategic deviation preferences based on cell coverage minimize contamination risks, as demonstrated in Figure 5 and Figure 6. However, attempts to optimize path deviations, as shown in Figure 7, reveal challenges in balancing contamination mitigation and distance factors.

Table 1 Mapping Intersecting Routes

Net	Man Dist	Int. Zone Covg.	Deviation Preference	Intersection Degree
A	13	15	1 √	3
B	16	48	4	3
C	13	44	3	3
D	9	1	5	1
E	7	10	6	1
F	12	17	2 √	3

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In the realm of Digital Microfluidic Biochips, synergistic routing approaches aim to manage droplets efficiently, particularly under combined routing conditions. By incorporating principles inspired by swarm intelligence, researchers seek to enhance droplet coordination.

Figure 5: Pathways with Adaptable Routes

Homogeneous droplets streamline analytical techniques, ensuring consistency in bioassays and resilience to transportation challenges. On the other hand, heterogeneous droplets pose complexities, especially when executing multiple bioassays simultaneously. Combined routing strategies, illustrated in below Figures, offer a holistic approach to optimize spatial efficiency and streamline bioassay execution, ultimately enhancing the diagnostic process.

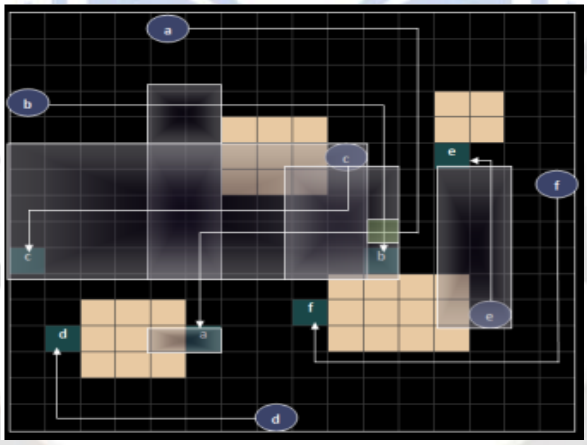

Figure 6: Avoidance Deviations in Route Zones

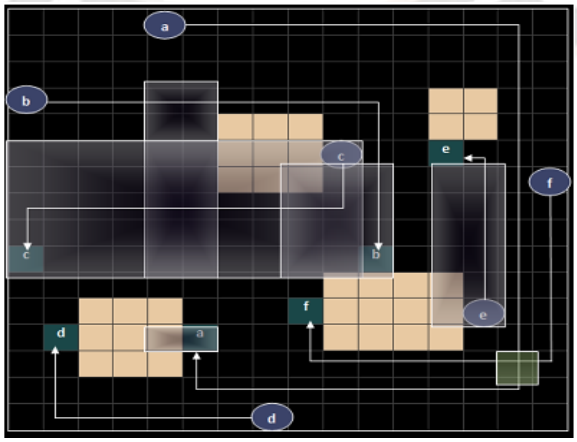

Figure 7: Exploring Additional Path Deviations for Net A

Result and discussion

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The study involves testing a specific algorithm using a testbench from the benchmark suite I. The focus is on a sub-problem called Test12_12_2, where a 12 x 12 2D layout for a digital microfluidic biochip (DMFB) is considered. The sub-problem involves 12 two-pin nets.

To evaluate the algorithm, three different cases (Case-1, Case-2, and Case-3) are examined, each representing a specific clustering of droplets in the DMFB. The clustering is based on homogeneity or heterogeneity of the droplets within each group.

In Case-1, droplets DO, D1, D3, D7, D9, and D10 are considered homogeneous and form one group, while D2, D4, D5, D6, D8, and D11 are heterogeneous and belong to another group.

In Case-2, the clustering is such that D0, D2, D4, D6, D8, and D10 are heterogeneous, while D1, D3, D5, D7, D9, and D11 are homogeneous.

In Case-3, the grouping involves D0, D1, D2, D6, D7, and D8 as heterogeneous, and D3, D4, D5, D9, D10, and D11 as homogeneous.

The route performance for each case is documented in a table labeled as 3, providing experimental results. This table likely contains information on the efficiency and effectiveness of the algorithm in handling the routing of droplets within the DMFB for each specific clustering scenario.

Table 2 Comprehensive Analysis of Results across Three Specified Scenarios

Test Bench	**Contaminations**			**Cell used**	**LAT (Latest Arrival Time)**	**AAT (Average Arrival Time)**
Test	**Heterogeneous**	**Homogeneous**	**Heterogeneous-Homogeneous**			
Case-1	**4**	**38**	**19**	**81**	**21**	**13.166**
Case-2	**3**	**46**	**22**	**79**	**23**	**13.166**
Case-3	**8**	**68**	**13**	**89**	**22**	**15.333**

In our research, we utilised Benchmark Suite III, which consists of four testbenches designed for route simulation employing the novel Route Zone-Based Technique. These test-bench's, namely In vitro 1, In vitro 2, Protein 1, and Protein 2, are composed of distinct subproblems, each representing a bioassay within a specific testbench. Our focus was on evaluating the route performance using key parameters, including maximum route time, average route time, number of contaminations, and the cells used. The results of these evaluations are presented in Table 3.

Table 3 provides a comprehensive overview of the performance metrics for the specified four test benches. These metrics are crucial in assessing the effectiveness of the proposed route-zone-based technique. The parameters considered, such as maximum route time, average route time, number of contaminations, and cells used, offer a holistic view of the simulation outcomes for each testbench.

Furthermore, our study extends to a comparative analysis presented in Table 3, where we juxtapose the route performance achieved through our proposed method with that of contemporary contributions. This analysis allows us to gauge the effectiveness of our technique in relation to existing approaches.

The key findings from our research indicate noteworthy improvements in both the latest arrival time and cell utilisation parameters when employing the proposed route-zone-based technique. These enhancements signify the efficacy of our approach in optimising route simulation outcomes. It is evident from the results that our method outperforms contemporary contributions, highlighting its potential for practical applications in bioassay simulations.

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Table 3 Insights from Benchmark Suite III Simulation Results

Test Bench				Heterogeneous Droplets		
Benchmark suite	**Sub-problems**	**2 pin**	**3 pin**	**Max route time**	**Total route time**	**Contaminations**
Protein 1	64	170	8	24	705	20
Protein 2	76	155	8	28	533.63	18
In vitro 1	11	20	6	20	126.09	2
In vitro 2	15	29	6	15	132.25	2

Test Bench	**Proposed Method**(CMRSD)			**Zhao and Chakrabarty**			**Huang, Ho, Lin**		
	Cntm	**T_{ex}**	**CPU**	**Cntm**	**T_{ex}**	**CPU**	**Cntm**	**T_{ex}**	**CPU**
Protein 1	20	705	2.98	18	1508	0.23	82	1394	2.58
Protein 2	18	533.63	2.05	11	1287	0.14	51	1108	1.49
In vitro 1	2	126.09	0.25	4	268	0.06	21	193	0.58
In vitro 2	2	132.25	0.30	0	224	0.03	6	191	0.39

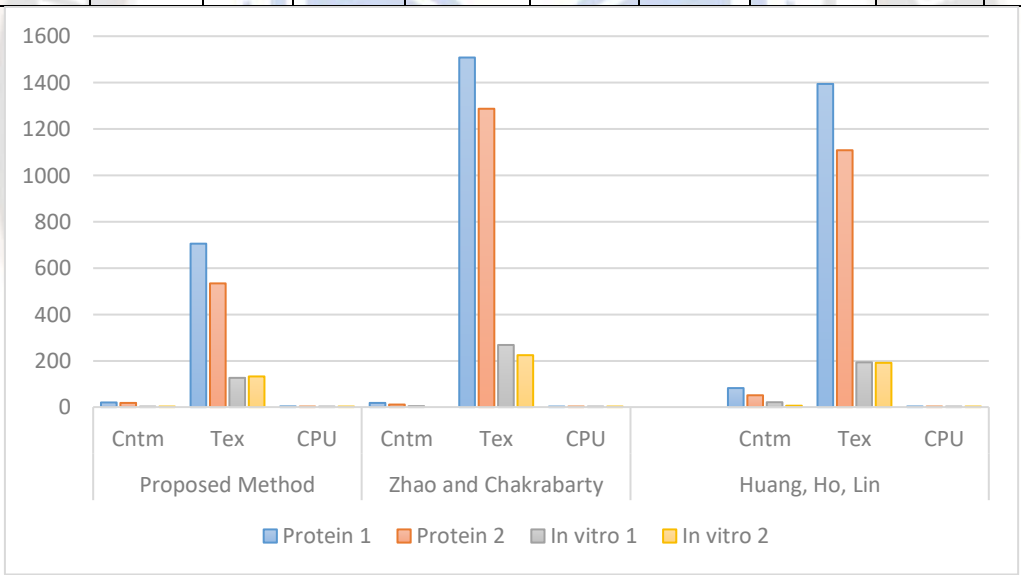

Figure 8 Comparative analysis with respect to the total number of contaminations, total route time and CPU usage

In comparing four test-benches with two widely cited contemporary works, the focus revolves around three key performance metrics: the number of contaminations, total arrival time, and cell utilization. The results indicate that the proposed method exhibits only marginal deterioration in terms of the number of contaminations. This marginal impact is attributed to a strategic decision made during the implementation process.

One noteworthy consideration was the avoidance of crossovers, which could potentially compromise the overall performance of the routing system. Despite this cautious approach, the proposed method ensures that other crucial aspects of route performance, specifically the latest arrival time and cell utilization, are not compromised.

Conclusion

In this research, the CMRSD algorithm emerges as a groundbreaking solution for optimizing droplet routing in DMFBs. By integrating concurrent routing, stalling mechanisms, and detouring strategies, this algorithm

significantly improves efficiency and robustness in droplet transportation. Experimental evaluations across various scenarios illustrate the algorithm's effectiveness in minimizing contaminations, optimizing route lengths, and enhancing overall route performance. Comparative analyses with contemporary methodologies underscore the superior performance of the CMRSD algorithm in terms of latest arrival time and cell utilization. These findings position the CMRSD algorithm as a pivotal advancement in the field of digital microfluidics, promising enhanced functionality and reliability for future bioassay applications.

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