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An Adaptive Low Cost Single Target Sample Preparation on Digital Microfluidic Biochips

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***Abstract*—Sample preparation on Digital Microfluidic Biochips (DMFBs) is an indispensable process for accomplishing biochemical reactions. Original reactants are usually diluted to the solutions with desirable concentrations. Framing various droplets with desired target concentrations on such a chip in an automated manner is the real challenge to sort out. In this work, we propose an Adaptive Sample Preparation Algorithm (ASPA) for DMFB. It can produce any sample droplets within the range of (0-1024) concentration factors (CF's) in an adaptive manner. The proposed method also ensures an error-free, cost-effective sample preparation for Digital Microfluidic Biochip (DMFB). Our method significantly reduces the number of sample droplets to prepare any single target concentration on a DMFB platform while the number of mixing-splitting steps remains the same for most of the cases compared to earlier methods. The requirement of buffer droplets and waste may be slightly more for a few cases in this method. However, as the buffer cost is negligible compared to fluid samples, the overall sample preparation cost decreases by our method.**

***Index Terms*—Digital Microfluidic Biochip, Sample preparation, Reagent, Concentration Factor, Adaptive**

I. INTRODUCTION

Digital Microfluidic Biochips replace the conventional complex biochemical process and also have the power to control the precise nanoscale volume of fluids like the sample, reagent, etc. The droplet can route on a 2-dimensional biochip in a discrete way [1]. DMFB is a new field of interdisciplinary research based on lab-on-a-chip (LoC) called as Total Analysis System(TAS) widely used in healthcare engineering and medical instrumentation domain [2]. Typically, an LoC can perform various biochemical in vitro test protocols (bioassay) on a single chip that is as small as a few square centimeters in size and which can provide low-cost and fast diagnostic solutions. In particular, droplet-based microfluidic biochips have gained wide acceptance in recent times for developing LoC applications in contrast to continuous-flow microfluidic chips. It uses electrical actuation to perform dispensing, transporting, merging, mixing, splitting operations on a droplet. Such a prototype chip has been used for clinical diagnostics, which includes more than 5000 electrodes. A commercial DMFB chip embeds more than 3 lacs of $(20\mu m \times 20\mu m)$ electrodes, acted as an integrated optical detector [3], [4]. The top-view of such a typical DMFB chip is depicted in Fig. 1.

In DMFB Synthesis, two important design optimization issues are in the area of routing [5], and mixing [6] to efficiently accomplish bio-protocols. Sample preparation of desired concentration is part of such bioassays [7] where dilution of a reactant fluid and mixture-preparation of several reactant fluids are two fundamental preprocessing steps. In diagnostic laboratories, off-chip samples are prepared manually and then put into the diagnostic machines which are susceptible to error due to human intervention and other experimental factors and take longer time and lesser throughput in comparison to automated on-chip sample preparation.

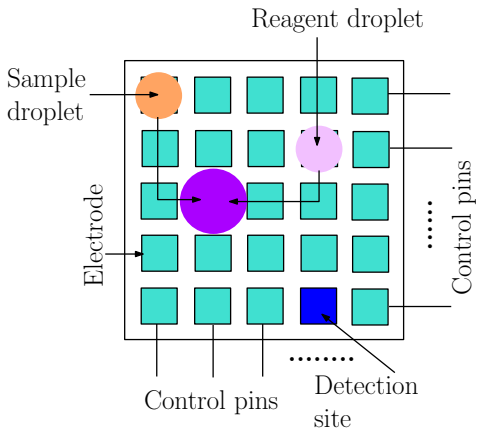

Fig. 1: Top view of a DMFB chip [4]

The majority of biochemical procedures are based on solution preparation. It is a primary step to prepare the sample or reactant at the desired concentration before combining it with another fluid. A biological sample/reagent must be diluted with the help of a buffer solution (called Diluent) to a desired concentration value [8] before mixing with another fluid. For In_Vitro testing, the dilution process has been used repeatedly to arrange different concentration ranges of solutions on a microfluidic device. Furthermore, for an effective bio-protocol, various assay activities (mixing, detection, mixing control, etc.) must be integrated on a single chip [8], [7].

Two types of dilution methods are used till date in DMFB platform. Serial (exponential) dilution and interpolated dilution [9]. A sample or reagent with 100% concentration is mixed with a buffer solution with 0% concentration repeatedly and the concentration of the solution reduces accordingly [8]. Hence, the new concentration factor of the solution is $(C_t = \frac{1}{2^n})$, where the value of n is 10_{10} and T_{ms} is denoted as the number of mix-split steps [9], [8]. Two equal shape and volume droplets are combined in one (1: 1) mixing phase, followed by a balanced split, resulting in the production of two same size droplets

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[8]. One mix, followed by a balanced split together, is called as a mix-split step. Hence, two droplets having concentration value C_1 and C_2 are mixed together and after splitting, two new droplets had been produced with same $(C_1+C_2)/2$ concentration values. The target concentration is considered as $\frac{x}{2^n}$, where $x \in \mathbb{Z}^+$, $1 \leq x \leq 2^n$ and n is equal to 10 in decimal. Now the target concentration factor (CF) can be achieved using a set of **P**rime **C**oncentration **V**alues **(PCVs)** recursively and in T_{ms} number of mix-split steps. Hence, the set of PCV values are represented as $\Phi(PCV) = \frac{2^i}{2^n}$, where i is $0 \leq i \leq 10$.

We propose a new on-chip dilution mechanism for preparing various concentration values on a DMF biochip. We initially start the dilution process with one sample droplet of extreme higher concentration value as $(1024/1024)$, called a sample droplet and another with the lowest concentration value $(0/1024)$, called as buffer droplet and subsequently, we add either a sample or buffer and try to achieve a single target concentration. Our proposed method can achieve any target concentration C_t within the entire range of (0 - 1024) using the minimum number of sample droplets compared to other mixing techniques and thus it can minimize the sample preparation cost as far as a single target concentration(sample/reagent/stock solutions) is needed on a DMFB platform.

II. Preliminaries

A. Architecture of Digital Microfludic Biochips

Several electrodes lying on a 2-dimensional Digital Microfluidic Biochips as shown Fig. 2. Droplets moved vertically as well as horizontally with the help of EWOD (Electro-wetting-on-Dielectric) on the DMFB [10]. The droplets are containing various types of biochemical samples, reagents, etc. Filler medium and droplets are resting in between two glass plates as displayed in Fig. 2. Different kinds of bio-assay operations (dispensing, routing, mixing, splitting, and detection) have been performed on the DMFB.

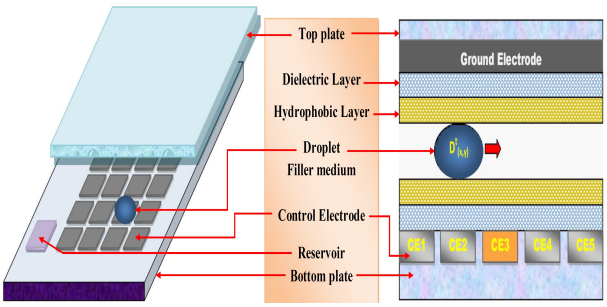

Fig. 2: Architecture of DMFB cell

B. Mix-Split steps of droplets:

Mainly two different kinds of mixing and splitting patterns had been followed. The first is "EVEN" mixing and splitting, whereas the second is "ODD" [11]. After 100% completion of mixing, if the mixer droplet is split into two equal volumes of droplets that is called "EVEN" mixing and splitting otherwise "ODD" is shown in Fig 3. It might be a (K: K) mixing model or a (1:1) mixing model. In [12] a 1:1 mixing pattern is described, in which X concentrated sample mixed with Y concentrated sample, resulting in two droplets of concentration $(X+Y)/2$ has appeared. It is represented by

$$C_t = (x+y)/2 \tag{1}$$

In case of unbalanced splitting, the entire volume of a solution may break into two unequal volumes of the resultant droplet. The balanced, as well as unbalanced mixing-splitting models, have also been shown in Fig. 3.

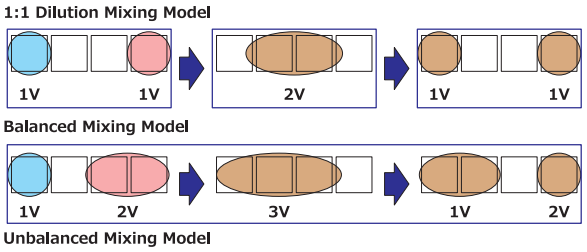

Fig. 3: Different Mixing Models for DMFB

C. Bit-Searching Method:

Bit **S**earching (BS) technique [13] is used to creates desired CF of a sample. The lowest concentration value (LCV) and highest concentration value (HCV) are 0 and 100 percent respectively. LCV and HCV is represented as $C_l = \frac{0}{2^n}$ and $C_h = \frac{2^n}{2^n}$ respectively and the value of n is 10 in decimal.

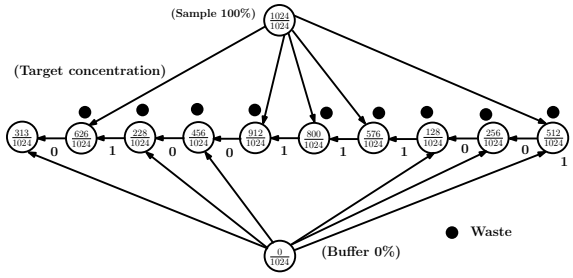

Fig. 4: Sample preparation sequence of $C_t = \frac{313}{1024}$ by using BS method [13].

Target CF C_t lies in between the HCV and LCV. To frame a particular dilution preparation, the BS method primarily finds the corresponding binary value of the sample with CF $\frac{313}{1024}$. Now the targeted CF has been converted to it's binary equivalent string as $\frac{313}{1024} = 0.010011101_2$. Hence the new string of the target concentration acted as a control word and it will describe the sequences of the dilution. BS method begins on the right-hand side of the binary string, ended at its decimal point. Initially, the sample is mixed with the buffer solution in a 1:1 mixing model after that the resultant droplet is mixed with sample or buffer that is decided by the binary bit. Binary bit '1' is specified for sample, on the other hand, '0' is specified for buffer. The desired dilution has been accomplished after ten stages as shown in Fig. 4. T_{ms} denoted as the number of mix-split steps used for the desired dilution preparation of the sample.

D. DMRW Method:

To handle a similar kind of problem, the DMRW technique [12] uses a binary search strategy. It checks if the desired

concentration (C_t) is higher or less than the present concentration value at each step. As the consequence, it executes a mixing and splitting step using the nearest upper or lower concentration value. DMRW works on the bottom-up strategy to obtain $C_t = 681$, for that it has been started with a sample concentration of $\frac{1024}{1024}$ and a buffer concentration of $\frac{0}{1024}$ as shown in example Fig. 5. $\frac{512}{1024}$ will be achieved in the first step of the mixing method.

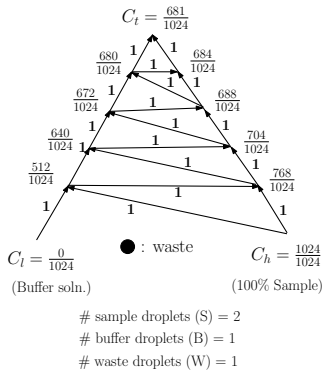

Fig. 5: Sample preparation of CF 681/1024 using DMRW method [12].

The numerator value of the target concentration is 681 which is more than 512. Hence we combine it with the next highest concentration 1024 to produce 768. In the very next step, if 681 is less than 768, we add 768 with the last lower concentration value $\frac{512}{1024}$ to obtain 704. 704 is now greater than C_t. This operation will be repeated until the desired concentration of 681/1024 has been reached. The number of droplets used for mixing as shown in Fig. 5 where the edges weight of the directed Graph decided the numbers of the droplets.

E. IDMA Method:

Waste savings based on the DMRW technique has been achieved using a heuristic-based dilution algorithm such as the Improved Dilution/Mixing Algorithm (IDMA).

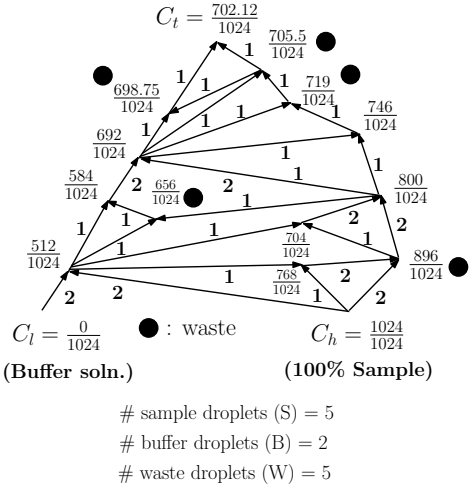

Fig. 6: Sample preparation of CF 702/1024 using IDMA method [4].

IDMA method initially takes two droplets as an input, one droplet with a lower CF C_l and the other with a higher CF C_h. After the first stage of the dilution, the target droplet C_t will produce maintaining higher degree of accuracy. Here lower CF is greater than zero but $\leq C_t$, similarly C_h is less than 1 but $\geq C_t$. Initially DMRW [12] is used to build the digraph M, then IDMA improves the digraph and uses the backtracking strategy to produce the target sample with the least amount of waste in Fig. 6.

III. Problem Formulation

We'll lay out our plan for creating single target concentrations in this section. Our major goal is to reduce the number of samples required to produce any single target concentration at the lowest possible cost as shown in Table I. The concentration factors (CF) are rounded off as n-bit fractional binary integers, with the range $1/2^n, 2/2^n, ..., (2n-1)/2^n$ omitting the given values CF = 0 and CF = 1. As a result, the issue may now be described as follows:

Given a set of k distinct targets $C_t = C_1, C_2, ..., C_k$ where $1/2^n \leq C_i \leq (2^n-1)/2^n$, for $i \in k$ generate C_t using only sample $C_{max.} = (2^n/2^n)$ and buffer $C_{minx.} = (0/2^n)$ droplets, such that the number of sample droplets have to be minimized.

TABLE I: Comparative study of sample-preparation with our method against the existing methods

Mixing algorithm	# Target CFs (# Droplets)	Minimization Protocol			Random input CFs
		T_{ms}	Wastage	Reactant usage	
Planar-array [14]	Unique (2)	No	No	No	Yes
Bit-searching [13]	Unique (2)	Yes	No	No	No
S. Roy et. al [12]	Unique (2)	No	Yes	No	Yes
Waste-aware [9]	Unique (2)	No	Yes	No	Yes
On-chip dilution [15]	Multiple (2)	Yes	No	No	No
PBDA [8]	Multiple (2)	No	Yes	No	No
REMIA [16]	Multiple (2)	No	Yes	Yes	No
NFSP [17]	One or more (2)	No	Yes	Yes	No
GDA, EGDA [18]	Unique (2)	Yes	No	No	Yes
IDMA [4]	Unique (2)	Yes	Yes	No	Yes
Proposed scheme	Unique (2)	Yes	Yes	No	Yes

In the conventional method if someone wants to prepare a sample with 30.056% concentrated solution then 3 sample droplets and 7 buffer droplets are required to achieve the desired concentration level as per the conventional method. After preparing the solution only one droplet is used for further experimentation. Hence, 9 droplets are wasted in a conventional laboratory procedure. Whereas preparing 30.056% concentrated solution in (1:1) mixing model, the concentration factor (CF) of target droplet to be almost equal to $\frac{313}{1024}$. Target CF is achieved by using several mix-split steps. Intermediate droplets which are not further used in the remaining process are called wastage. To achieve desired CF with using the minimum number of very costly samples (highest CF = $\frac{1024}{1024}$) is the real challenge for the sample preparation problem. The number of $(1:1)$ mix-split operations should also be minimized as a secondary objective and the number of waste droplets minimization is targeted as the triennial goal.

IV. Proposed Mixing method

In our proposed method target CF is represented as C_t. At the first stage, we compare the C_t with $\Phi(PCB)$, if they are equal then we only calculate the buffer and wastage to achieve target dilution. On the other hand, if it is not equal then we multiply

C_t with 2 and the closest PCV value is found out. This value is subtracted from PCV and then the binary logarithm of the result is taken. If the output of the logarithm turns out to be an integer value then it is with the set of $\Phi(PCB)$, otherwise, continue the above process recursively. Iteratively the next PCV value is calculated to get the exact digraph of the target concentration. Now the resultant concentration C_t for the process is achieved after some iteration.

Most of the mixing techniques on the DMFB platform have used a tree-like structure to represent the mix-split steps. Such trees are called dilution tree [19] and to remove the error in the mix-split steps and to frame the exact concentration value required pruning technique [9] is used on such dilution tree which is an overhead to the total mix-split time. Our proposed technique is based on a directed graph G where we started with only one sample and one buffer droplet rather than taking multiple sample droplets as tried in DMRW [12], IDMA [4] in the initial phase. Later as per requirement, we will add sample droplets dynamically when it is absolutely necessary. Thus we can reduce the use of sample droplets which are excessive costlier compare to buffer solutions. In IDMA [4] at the very initial stage more than one PCV value is combined to get the target concentration. On the other hand, ASPA does not use it at the beginning, rather at the very next stage, an adaptive process (in the form of the binary logarithm) is used to save the sample droplets. Using such calculation ASPA can reduce the cost of sample preparation.

Initially, we have generated all the Prime Concentration Values $\Phi(PCV)$ as per the following formula:

$$
\begin{aligned}
Y_1 &= (C_s + C_b)/2 \\
Y_2 &= (C_s + C_b)/2^2 \\
Y_3 &= (C_s + C_b)/2^3 \\
&\vdots \\
&\vdots \\
Y_n &= (C_s + C_b)/2^{n-1}
\end{aligned}
$$

Where $Y_n \in \Phi(PCV)$ and C_b is buffer solution with minimum CF ($\frac{0}{1024}$). Thus we obtain various $\Phi(PCV)$ values $512 \rightarrow 256 \rightarrow 128 \rightarrow 64 \rightarrow 32$..... from the highest concentration factor C_s which is $(1024/1024)$ in our case.

Our method initially takes the desired target concentration C_t as input. Then it computes the exponential value after being multiplied by 2 to find the nearest PCV which is represented by P as shown in Equ. 2. The value of P may be a floating-point or an integer. P also indicates that the C_t belongs to PCV or not. If the value of P is a positive integer then C_t definitely belongs to the set of $\Phi(PCV)$. Otherwise, our method has to set the new value of C_t using m from Equ. 3. The truncated integer value of P is represented by m and also $m \in \mathbb{Z}^+$. Hence, the new value of C_t is returned recursively for finding P which is equal to $(2 \times C_t$ - $2^m)$.

$$P = log_2(2 \times C_t) \tag{2}$$

$$m = int(P) \tag{3}$$

New value of C_t is multiplied with 2 and becomes $(2 \times C_t)$ then it will find the nearest PCV value. Hence, it will subtract from the nearest PCV value. This process will continue till the $C_{t_{Final}} = 2 \times C_t - PCV$ becomes a new set of $\Phi(PCV)$. The proposed flow chart and algorithm for the adaptive sample preparation algorithm (ASPA) as shown in Fig. 7 and 1 respectively.

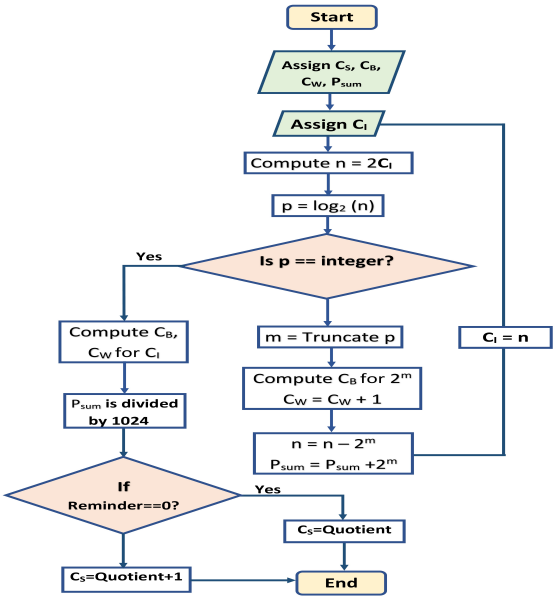

Fig. 7: Flow chart of Adaptive Low Cost Single Target Sample Preparation Algorithm (ASPA)

For example if we want to produce the target CF of f(1) = $\frac{313}{1024}$ and f(2) = $\frac{702}{1024}$ using ASPA are as follows. Here $C_t(1)$ and $C_t(2)$ are the numerator values of f(1) and f(2) respectively. Now the present values of $C_t(1)$ and $C_t(2)$ are not the set of Φ(PCV). Hence, $C_t(1)$ and $C_t(2)$ are multiplied by two. Hence, compute the value of P for the resultant values 626 and 1404 respectively from the Equ. 2 which are 9.290018846932618 and 10.45532722030456 respectively. Next step of ASPA computes the value of m from the Equ. 3. It has been shown that m is the integer part of P and it becomes 9 and 10 respectively.

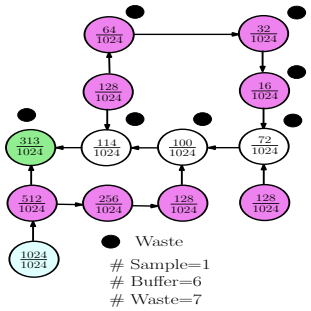

Fig. 8: Sample preparation of CF 313/1024 using our method

Thus, the new $C_t(1)$ and $C_t(2)$ values for the process is $(2\times\ C_t(1)$ - $2^m)$ and $(2\times\ C_t(1)$ - $2^m)$ which are 114 and 380 respectively as shown in Fig. 8 and Fig. 9. Sample droplets required for the PCV values to get the exact digraph of the target concentration are as shown in Fig. 8 and Fig. 9.

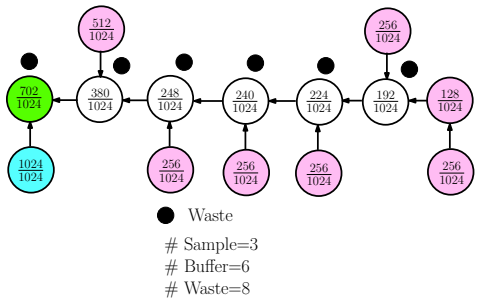

Fig. 9: Sample preparation of CF 702/1024 using our method

Algorithm 1: Adaptive Sample Preparation Algorithm (ASPA)

Procedure ASPA(n):;
Declare $C_{max.}$, $C_{min.}$ and ϕ(PCV);
/* $C_{max.}$ = Sample ($\frac{1024}{1024}$) $C_{min.}$ = Buffer ($\frac{0}{1024}$); ϕ(PCV) = $\frac{2^i}{2^{10}}$, $0 \leq i \leq 10$ */
Input: Target CF (C_t);
Initialize $S_{count} \leftarrow 0$; $B_{count} \leftarrow 0$; $W_{count} \leftarrow 0$;
/* S_{count} = Sample count; B_{count} = Buffer count; W_{count} = Waste count; */
Set $P_{sum} \leftarrow 0, T_{MS} \leftarrow 0$;
/* T_{MS} = Mix-spit step count; */
if $C_t = \phi(PCV)$ **then**
    Goto step PCV();
    Compute n = 2*C_t;
    Compute P = log2n;
else
    while $P! = int.$ **do**
        $m \leftarrow truncate(P)$;
        $P_{sum} \leftarrow (P_{sum} + 2m)$;
        n = (2n - 2m);
        enumerate T_{MS} for 2m and increment by 1;
        Modify B_{count} and W_{count} for 2m;
    end
end
Compute S_{count} = $\frac{P_{sum}}{1024}$;
if P_{sum} % 1024 == 0 **then**
    S_{count} = int(P_{sum} / 1024)
else
    S_{count} = (S_{count} +1);
end
PCV():
    Calculate B_{count} and W_{count} for 2^i;
    S_{count} = (S_{count} +1);
return

Now the resultant concentration 114 and 380 are achieved after some iteration. After one or more iteration when the resultant values P are equal to the set of Φ(PCV), ASPA will end the process after calculating the number of samples, buffer droplets required and total wastage for the entire sample preparation process. In the above examples $\frac{313}{1024}$ and $\frac{702}{1024}$, the number of samples and buffer droplets required are 1,6 and 3,6 respectively. Total waste droplets for the entire process are 7 and 8 respectively.

V. Mixing Architecture

A novel DMFB architecture for 1:1 mixing model has been proposed for sample preparation using ASPA as shown in Fig. 10.

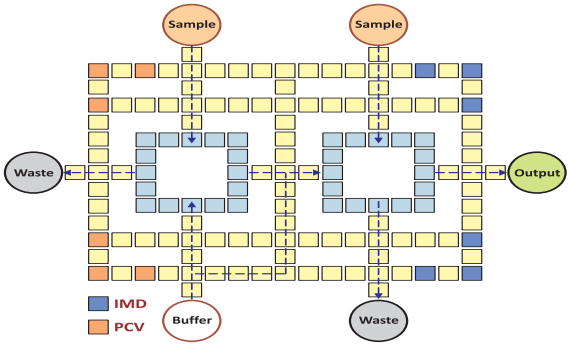

Fig. 10: Mixing Architecture

There are three types of 0^0 shift-movements and 90^0-shift pattern used to accomplish mixing operation. 0^0_1-shift is read as first-order zero degrees shift similarly 0^0_2-shift is represented as second-order shift and 0^0_3-shift means third-order shift which is linear shift along with three consecutive cells as seen in our proposed architecture. Completion mixing percentage after each shift has been calculated from MLS [6] and RBS method [20]. Step count and time required to accomplish one mixing step for ASPA are 28 and 1.8secs respectively which is also less than the existing works.

VI. Result Analysis

Our primary objective was to prepare any single target concentration with the minimum number of sample droplets. In our simulation experiment with ASPA, samples required for the range of 1-341, 342-681, 682-768 and 768-1024 are shown in Table II. We have compared our method ASPA with the earlier mixing techniques BS [13], DMRW [12], IDMA [4] and REMIA [16] as shown in Table III. We find out the number of samples and buffer droplets used for the entire dilution range from $\frac{1}{1024}$ to $\frac{1024}{1024}$ as shown in Table II. We have analyzed the required number of Mix-Split steps and Sample droplets for 16 arbitrary concentration values are as shown in Table III.

TABLE II: Concentration vs. Nos. of Samples

Concentration Range	Number of sample droplets used
1-341	1-2
342-681	2-3
682-768	3-4
768-1024	4-9

Simulation result using ASPA found that most of them can be prepared only with one sample, except in 3 instances $\frac{251}{1024}$, $\frac{513}{1024}$ and $\frac{702}{1024}$ as depicted in the Table III. For these three instances, the number of samples required is equal to or even lesser than other methods. Only for one instance $\frac{251}{1024}$ REMIA [16] can perform better than ASPA but otherwise ASPA complete with the prior art as well delineated in Table III. From Table II it can be seen that for some specified concentration range or within a particular range (1 - 341), ASPA can generate all the CF by utilizing one or two sample droplets. Hence, for the concentration range (342 - 681), 2 sample droplets are needed.

TABLE III: Selection of the best method for sample minimization in case of some target CFs

Target CF, C_t	IDMA [4]		DMRW [12]		BS [13]		REMIA [16]		Our Method		Best scheme (in res. to sample)
	S_1	T_{ms}	S_2	T_{ms}	S_3	T_{ms}	S_4	T_{ms}	S_5	T_{ms}	
$\frac{16}{1024}$	1	6	1	6	1	6	1	6	1	6	ALL
$\frac{127}{1024}$	1	11	1	14	7	10	1	14	1	11	ASPA/REMIA
$\frac{251}{1024}$	1	17	1	13	7	10	1	13	2	15	REMIA
$\frac{256}{1024}$	1	2	1	2	1	2	1	2	1	2	ALL
$\frac{259}{1024}$	2	17	3	15	3	10	2	10	1	16	ASPA
$\frac{261}{1024}$	2	17	3	13	3	10	2	10	1	15	ASPA
$\frac{263}{1024}$	2	15	2	16	4	10	2	11	1	15	ASPA
$\frac{264}{1024}$	2	16	2	10	2	7	1	7	1	12	REMIA/ ASPA
$\frac{267}{1024}$	2	16	3	13	4	10	2	10	1	13	ASPA
$\frac{268}{1024}$	2	16	3	11	3	8	1	8	1	12	REMIA/ ASPA
$\frac{269}{1024}$	2	13	3	14	4	10	3	11	1	14	ASPA
$\frac{313}{1024}$	2	15	3	18	5	10	3	11	1	13	ASPA
$\frac{327}{1024}$	2	17	3	18	5	10	3	11	1	16	ASPA
$\frac{341}{1024}$	2	10	1	10	5	10	2	10	1	11	ASPA/DMRW
$\frac{513}{1024}$	2	10	6	14	2	10	3	10	2	11	ASPA/IDMA
$\frac{702}{1024}$	5	17	6	16	7	9	3	12	3	8	ASPA

From 682 to other higher CF values though more number of samples are necessary still ASPA is used a lesser number of sample droplets than the earlier discussed mixing techniques.

VII. CONCLUSIONS

Our method can produce any single target concentration only with 1 or 2 droplets within a specific range and it minimizes the use of costly sample droplets to produce any target concentrations compared to other available mixing methods. Though in some cases the number of mix-Split steps and waste generation is more sample cost can be reduced. To apply this method for multi-target concentration generation and also to minimize the number of buffers and mix-split steps along with our primary objective of sample minimization can be the future scope of this work.

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