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AI-guided Automated Sample Preparation Advantages in Micro Electrode Dot Array (MEDA)-based DMFB over Microfluidic Biochips: A Comprehensive Review

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ABSTRACT
Timely completion of complex bioassays with absolute accuracy and minimal human intervention is a challenging task. Considering their sensitivity, sample preparation plays a crucial role in any bioassay protocol for efficient clinical diagnostics and functioning of Point-of-Care (PoC) devices. Conventional Digital Microfluidic Biochips (DMFBs) adopt a unit volume droplet mixing model to get the desired target concentration. To achieve the target concentration, fixed-size volumetric samples are used, and a positive integer mixing ratio is applied to get the concentration factor. However, volumetric error loss during splitting is inherent and may alter the concentration profile. Significant research is carried out on resource-limited sample preparation techniques and optimization on Micro-electrode Dot Array (MEDA)-based biochip in an automated manner. In MEDA-based sample preparation, the existing algorithmic design is used for dilution tree preparation in an automated manner. Both sample and buffer droplets of any size ratio can be merged, mixed, and diluted to get the target concentration factor for successful bioassay execution. On the MEDA-based platform, the manipulation of the fractional volume of costly samples (enzymes or similar bioanalytes) in a nano (10^{-9} L) or picolitre scale(10^{-12} L) is also possible, thus minimizing volumetric error in splitting steps over conventional mix-split.

MEDA offers low-cost, strategic Point-of-Care (PoC) applications, DNA and RNA sequencing, immunoassays, and toxicity analysis in real-time on a module-based platform. Emerging applications of new-age Artificial Intelligence (AI), like machine learning, reinforcement learning, and neural network-inspired algorithms, will create a revolution in conventional disease diagnostics in a highly accurate manner and may make a game-changer in the biochip revolution also. This review work highlights the existing sample preparation techniques, architecture, and improvement on different algorithms in resource-limited single and multi-target concentration synthesis.

Keywords
Sample Preparation, Bioassay, Mixing, Micro-electrode Dot Array (MEDA), Biochip.

1. INTRODUCTION
Recent advancement in microfluidic technology has gained significant momentum in bio analytical assay formulation designing and become an appropriate replacement for expensive and cumbersome bench top laboratory setup facilitate higher throughput and accuracy [1]. Biochip have emerged as pivotal analytical devices for completion of different bioassay with the highest degree of accuracy in the shortest possible time. Biochip based bioassay finds its significant application in molecular biology immunological application, biomedical and in vitro tissue based research, point-of-care analysis, clinical drug and toxic element analysis and many more applications yet to be explored. Micro-electrode -dot -array (MEDA) based biochip use nano or picoliter volume of expensive reagents and samples to complete bioassay with greater degree of accuracy in an automated way thus reducing human intervention, reagent consumption and error rate. Basic principle for droplet migration in 2D electrodes is based on the phenomenon of electro-wetting on dielectrics (EWOD) in which changes in voltage actuation across electrodes is used for droplet merging, mixing, splitting and dispensing like operation on biochip. The cross-sectional and top view of a typical DMFB is shown below in Fig. 1.

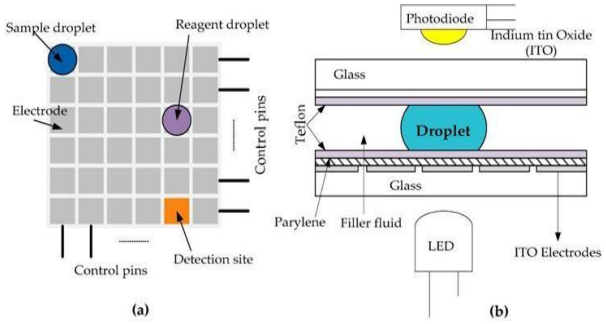

Fig. 1: EWOD-based digital microfluidic biochip. (a) Cross-sectional 2d architecture. (b) Top view of droplet migration on a single DMFB cell

Sample preparation is the most integral part of any protocol-based bioassay execution. Most of the droplet-based DMFB (digital microfluidic-based biochip) architecture supports mixing-splitting of fixed volumetric ratio of sample: buffer(x:y,x≠y), mostly (1:1) as a positive integer value to get the target concentration. Inherent volumetric loss fraction of $(1/2^{n+1}$, n: mixing-split steps may affect resultant concentration.

Digital microfluidic-based biochip (DMFB) architecture although perform fluidic operations (module placement, droplet merging, mixing, splitting, dispersion), still droplet size flexibility, fabrication process and sensor integration and real time droplet position sensing were the major challenges. MEDA architecture conceived as sea of microelectrodes overcome DMFB-based fluidic operations limitation through

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scalability, high configurability, and fully programmable, automated on-board sample preparation through dilution graph generation.

Major improvements in sample preparation in MEDA architecture include fast lamination mixing [2], diagonal droplet movement for better bioassay execution, CMOS circuit-enabled real-time droplet position mapping, fully programmable control of individual electrodes for detour of droplets in case of degraded or charge-trapped microelectrodes.

Li et al [3] introduced dilution graph (DG) based sample preparation through droplet sharing and proposed weighted sample preparation algorithms (WSPM) which is more efficient over earlier sample preparation algorithms like bit scanning methods (BS)[4], the algorithm for dilution mixing with reduced wastage (DMRW)[5], improved dilution mixing algorithms (IDMA), and also the reactant minimization algorithm (REMIA) [6]. Also, a module-less sample preparation technique, along with mixing and synthesis, is also proposed by Chakraborty et al. [7]. The synthesis steps for a typical bioassay on a DMFB are consist of various stages as shown below in Fig. 2 .

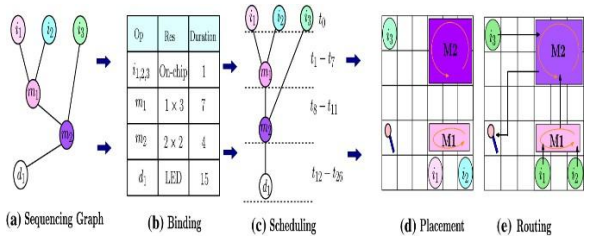

Fig 2: Synthesis steps for typical bio-operations on DMFB

This paper identifies the various available sample preparation algorithms for DMFB and their improved AI-guided automated versions, proposed to date by different research groups, and extensively analyzes each work. The comparative analysis of different MEDA-based sample preparation techniques are done, and it highlights their respective advantages and disadvantages and technical challenges to implement those algorithms on MEDA-based DMFB.

2. PRILIMINERIES

Consider reagent and buffer droplets having size of S_1 and S_2 with concentration factors of C_1 AND C_2 are getting mixed in mixer module of size M, resultant droplet concentration will be of $Ci=||S_1C_1+S_2C_2||/(S_1+S_2)$, where $M< (S_1+S_2)$ satisfy maximum size constraint for efficient droplet mixing. Simulation data comparison revels WSPM significantly reduces sample dilution during sample preparation on MEDA based biochip over other sample preparation algorithms.

In DMFB based sample preparation, unequal volume droplet split post mixing is major source of drift in target concentration factor (CF, 0<CF<1). Single and multiple level unbalanced volumetric split error reaches its maximum value poses critical steps in sample preparation. Algorithmic solutions for CF error identification is critical for identification and intermediate droplet rollback to get near target CF [8].

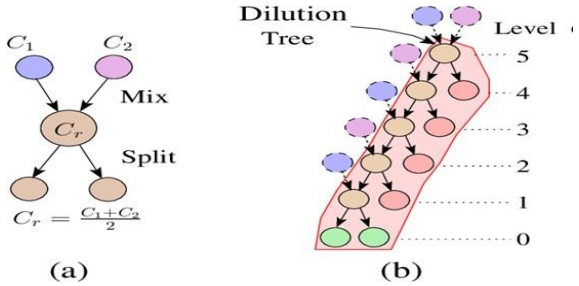

Fig 3: (a) Sample dilution and target concentration through mixing unit volume of sample: buffer (1:1) in serial dilution. (b)Dilution tree generation with number of mixing steps as level marked.

Liang et al.[9] introduced RL(reinforcement learning) based novel framework based multi target sample preparation using multiple reactant cost minimization (MRCM) as mixing models via droplet sharing. Further improvement results in enhanced MRCM (eMRCM) further explore sharing of droplets in dilution tree to get target concentration via reduction in reactant cost, mixing time and waste generation.Overall target concentration factor sample synthesis optimization consider following parameters (i) sample cost minimization[10].(ii) reduced mix-split cycle time[11](iii) reactant and waste minimization[12](iv) droplet size aware volumetric error correction [13].

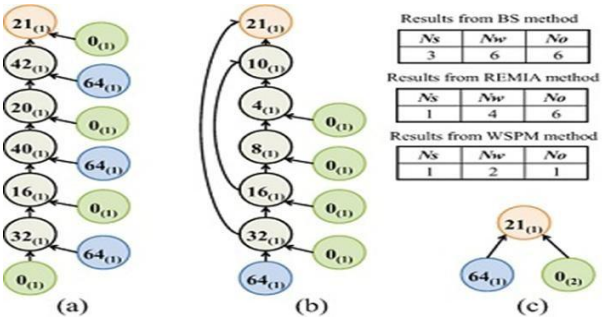

Fig 4: Automatic Sample dilution graph to reach target concentration using (a). Bit Scanning (BS) (b). Reactant Minimization Algorithm (REMIA) (c). Weighted Sample Preparation (WSPM) [13]

In the past, several volumetric error recovery strategies are introduced to tackle the issues of electrode degradation, charge trap and droplet uneven split, both offline [12] and online but were unable to fulfill the respective purposes [8, 9, 10, 11]. MEDA overcome such concentration error-relevant issues by adopting flexible droplet sizing and multi- directional and diagonal droplet migration using dynamic electrode placement architecture and reconfigurable routing. MEDA offers error-tolerant sample preparation by adopting aliquot mixing, thus bypassing droplet split related volumetric error and generation of parallel multiple dilution of sample [13].

Desired sample preparation in time bound manner considering sensitivity of bioanlytes (enzymes/small proteins and peptide) with precise concentration is the most challenging task. Both samples and buffer droplets are merged, mixed and split under controlled actuated voltage signal. Various volumetric mixing ratios (sample: buffer: m:n, m≠n) adopted to synthesize target concentration factor (C_f= m+n /2) assume droplets of same size of 1X volume. Corresponding linear dilutions of samples generate dilution tree as mix-split tree for particular C_f as **($1/2^n$)** where n denotes number of dilution steps[14].

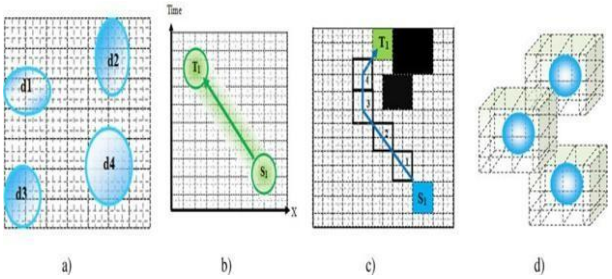

Fig 5: a) Different sizes droplet in MEDA based layout. (b) Euclidean distance between droplets d from source to target position. (c) Droplet migration from sourceS1-T1 in 2D view to droplet pathway. (d) Movement of droplet in 6x6 cells in 3-D view [35]

In MEDA enabled biochip, both samples and buffer droplets of different sizes are getting mixed in certain specified concentration ratios, creates dilution graph based sequential tree for target concentration and execution of bioassay in programmed manner. MEDA offer fractional volumetric mix-split over unit volume sample to buffer, uses less mixing steps, to get concentration value. Integer linear programming (ILP) based MRCM (multi reactant cost minimization) algorithms generate waste efficient dilution tree to get CF [15]. MEDA offers dynamic architecture, better configuration and fluid management using control signal to individual electrodes for functional optimization.

3. LITERATURE REVIEW

3.1 Mixing models for automated sample preparation in MEDA-based biochip

Primary objective of Sample preparation for any bioassay involves dilution of stock to target concentration through successive dilution. Different volumetric ration of droplets of various sizes are mixed in sequential stages. For N number of mixing operation, positive integer partition of 2…..(n-1),n. examples includes Mix-4 support (1:1:2,2:1:1, 1:3,1:2:1) and mixing stages depends on maximum upper limit of mixer size(M). So p number of droplets of each volume v_i having concentration of c_i are mixed-split and resultant concentration factor C_f will be :

For single target C_f synthesis with waste minimization, single target waste minimization model generates mixing tree for maximum intermediate droplet sharing thus waste minimization is lowest level[15].

Li et al.[16] published droplet size aware and error correcting sample preparation in MEDA enabled biochip architecture where droplets of size S_i and Sj,concentrations C_i and C_j mixed, target $\mathbf{C_f= (S_iC_i+S_j)/(S_i+S_j)}$, $\mathbf{M_v< S_i+S_j}$ where M denotes mixer volume in MEDA. Liang et al.[16] published comparative analyis in mixing models for multi-target sample preparation on DMFB and MEDA, optimized using multi-reactant cost minimization algorithm(MRCM) for waste efficient mixing.

Kundu et al.[17] highlights single target waste minimization algorithm based mixing model optimization works efficiently over division by factor(DFM) based algorithm for reactant and waste minimization, reduction in mixing cycle time.

Kundu et al.[18] published reinforcement learning (RL) techniques for reliability aware heuristic approach for droplet placement and collision avoidance algorithm (CAMR),that identifies collision free droplet routing of different volumes for efficient mixing. Powerful RLPM (reinforcement learning placement method) algorithm reduces available chip area and total bioassay completion time.

3.2 Generational Improvement in MEDA-based Biochip, Structural and Technical advancement

Over the year, Significant improvement in MEDA architecture considering minimization of droplet routing area, avoidance of cross contamination, charge trap and micro electrode degradation due higher threshold voltage and precised droplet control on 2D architecture makes it more user-friendly. MEDA biochip comprises of system control unit and micro electrode control unit where individual cells are connected as daisy chain[25].

1st generation MEDA biochip [19], user interlined wire-based interconnection among micro-cells and no optical or capacitive based sensing unit for droplet control mechanism do exist.

$$cf = \frac{v1xc1 + v2xc2 + \cdots \ldots vixci}{v1xc1 + v2xc2 + \cdots \ldots vixci}$$

The algorithms for sample dilution on MEDA biochip optimize mixing steps for generation of mixing tree. Target concentration optimization involves, less fluid wastage, less reactant uses and reduction in mixing steps. The depth (accuracy) of mix-split tree is $^1_{2^{n+1}}$to get target C_f.

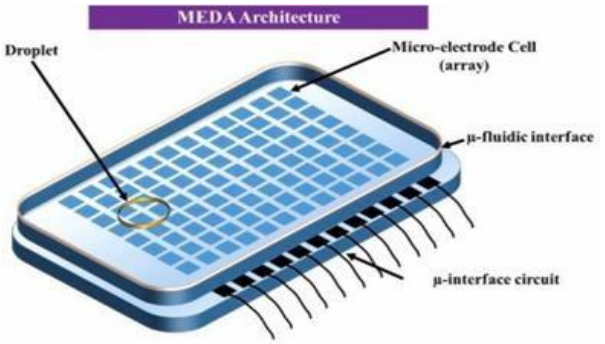

Fig 6: Top view of 1st generation MEDA biochip.[30].

2nd generation MEDA biochip [20], a CMOS enabled upgradation, where droplet sensing and controlling circuit were fully integrated, resulting in size and position based optical or capacitive based droplet sensing on 2D location map. Improvement in fluidic mobility, enhances smoothness and reliability in droplet manipulation and routing.

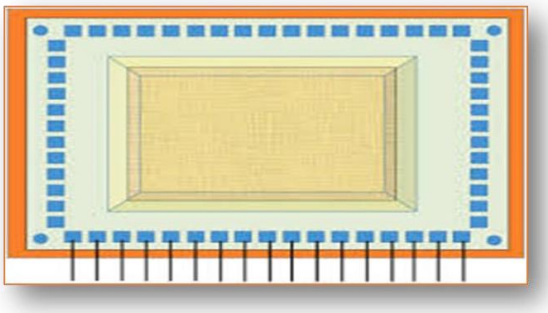

Fig 7: 2nd generation MEDA biochip improvement

MEDA biochip of 3rd generation offer higher voltage capacitance for individual microelectrode cell of 25V

surpassing 14.5V breakdown voltage for 2nd generation, resulting in efficient droplet control [21]. Enhanced resolution of 5fF in comparison of earlier biochip (1.3fF) gives precise 2D location based droplet mixing operation and improvement in sensing circuit [22]. Also, energy efficient (40%) improvement in power consumption for droplet routing performance gives better mileage over second generation predecessor. Logic 1 for cell activation and logic 0 for deactivation, X for cell blockage makes 3rd generation MEDA biochip more control logic efficient [19,23,24].

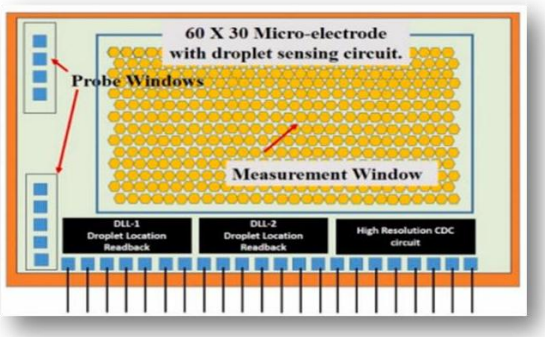

Fig 8: Third generation MEDA based biochip[30].

3.3 Droplet Splitting Tree-based Multi Concentration Sample Preparation Considering Reactant and Waste Minimization

Significant improvement in sample preparation techniques on MEDA based DMFB architecture for implementation of wide ranges of bio protocol-based bioassay is gaining momentum in point of care diagnostics including accuracy of target concentration, reduction in mixing cycle timing and droplet routing are some of key research areas. Adaptive sample preparation algorithm (ASP) for low cost single target concentration generation was proposed by [27] can generate sample concentration in the range of 0 to 1024 in comparison with existing algorithms more efficiently. While number of mixing splitting steps are same indicates reacting timing improvement for droplet routing is another challenging area. Also ASP does not focus much on volumetric error generated during uneven splitting on MEDA.

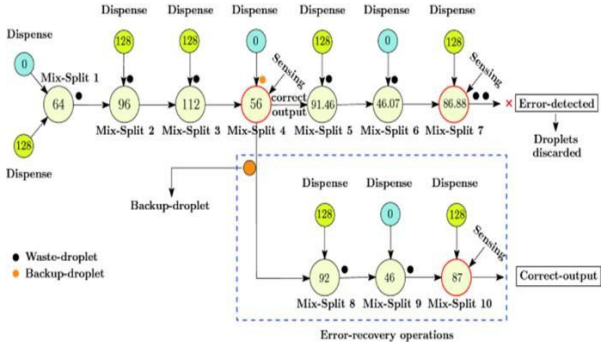

Fig.9: Volumetric error generated due to unbalanced splitting causes mismatch in the target concentration factor (CF) [8].

3.4 Methodologies Used for Waste-Minimization during Sample Preparation

Further development in sample preparation in terms of both reactant and waste minimization by generating splitting droplet tree based sharing algorithm approach is another efficient technique for target concentration generation concurrently proposed by [6]. All existing sample preparation algorithms fail to achieve gradient dilutions with minimum volumes of samples used and volumes of waste generation. Splitting droplet sharing algorithm (STA) begins with ration decomposition stages followed by splitting graph construction to get single target concentration. Dilution gradient profile generation created by considering sample ($2^p/2^p$) and buffer ($0/2^p$). Target sequence of target concentration profile (CF) can be generated as $\{2^p/2^p, 2^{p-1}/2^p, \ldots\ldots 1/2^p, 0/2^p\}$using STA. overall STA outperform existing REMIA [29] in terms of volume of sample used and waste generation although little highlights on minimization of available chip rea used for routing and volumetric error due to uneven droplet sharing.

3.5 Droplet splitting omitted and error tolerant multi target sample preparation on MEDA biochip:

Conventional sample preparation using whole sample and droplets are merged, mixed and split, resulting in volumetric error distribution due to uneven split. Instead, only fractional volume (aliquots) of droplets are merged and mixed. So differential size aliquots give multiple copies of target concentration factor without splitting [25]. Differential size aliquot mixing also takes no extra time for volumetric error recovery and sensing operations. Cost effective and fully parallelized multiple copies of sample preparation is possible without sharing intermediate droplets. Earlier all multi target sample preparation involves intermediate droplet sharing, not suitable for fault tolerance and parallelization.

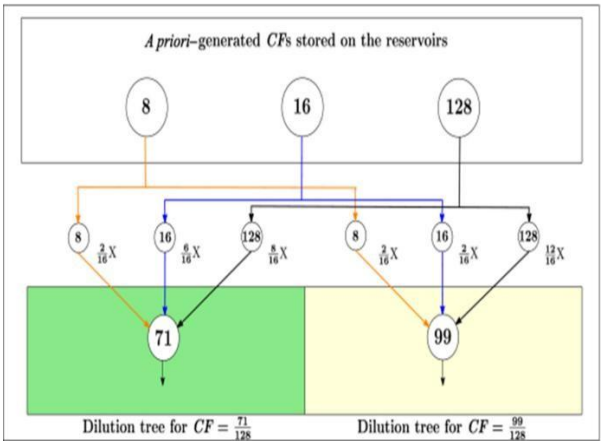

Fig 10: ILP based multi target CF (71/128) synthesis without split using priori generated CF stored in reservoirs sourced from scholarly work authored by Poddar et al [18]

Minimization of waste droplet generation is also primary objective of bioassay protocol because expensive reagents used. Earlier sample preparation algorithms focused on minimization of mix-split steps by intermediate droplet sharing [26, 31].

Integer linear programming (ILP) based sample preparation

approach by [25] gives multiple copies of target CF ($1/2^p$, p is positive integer) without splitting.

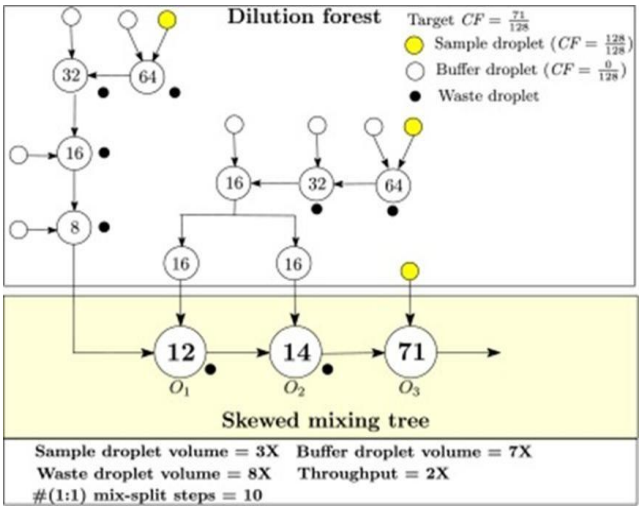

Fig 11: Dilution forest-based target CF (71/128) for accuracy level 7 using traditional DMFB using REMIA [29].

4. AI-GUIDED SAMPLE PREPARATION TECHNIQUES ON MEDA-DMFB:

In contrast to DMFB, droplet routing complexity in MEDA increases due to simultaneous handling of droplets of different sizes and repeated utilization of microelectrodes on MEDA architecture. Minimizing use of costly reagents and waste droplet generation, and reducing in mixing cycle within small chip area further escalates droplet collision and contamination chances. The MEDA based biochip can move droplets diagonally through utilization of interim bridging steps. Bridging process acts as connecting lines between electrodes form smooth droplet migration.

Liang et al [30] proposed a novel framework for reinforcement learning (RL) based droplet routing on DMFB. Experimental finding suggests while electrodes on DBFB degrades gradually, RL can adapt electrode degradation pattern and transport droplets through functional electrodes only. RL enabled droplet routing on MEDA architecture cuts droplet routing timing, reduced volume of droplet utilization thus accelerates successful sample dilution to achieve target concentration.

Kundu et al. [18] proposed two phase synthesis techniques for optimal droplet routing to improve reliability of biochip. First RL based reliability aware rectilinear shaped microfluidic module placement and heuristic based routing for droplet collision avoidance. RLPM (reinforcement learning based module placement) based on action -reward based droplet migration to avoid charge trapped or nonfunctional electrodes while increasing reliability by using less chip area.

Collision avoidance droplet routing initiates by optimizing parameters includes maintain fluidic constraints i.e no to droplets touch each other on same pathway or in adjacent cells on same timestamp, so that unit volume of droplet always find escape route. Following parameters like total route length, total route cost and total routing time are optimized for successful sample preparation. Overall, both RLPM and CAMR (collision avoidance microelectrode routing) improves available biochip area utilization and less reaction time.

5. TECHNICAL CHALLENGES IN MEDA-BASED INTELLIGENT BIOCHIP IMPROVEMENT

With the advancement of technology and increasing population, the demand in the rapid point of care biochip raises in clinical diagnostics, toxicity and various immunoassay. Automatic cost-effective sample preparation with target concentration for successful completion in shortest possible time is challenging filed of research. Also minimization of cross contamination during fluid handling through same architecture possess major challenges in biochip design.

Numerous research is carries on advancement in algorithmic approach in sample preparation techniques as it is first stages for any protocol based bioassay execution. MEDA based biochip offer precise control in droplet sensing and laminar mixing. Active CMOS logic circuits control microelectrodes thus can sense droplet position and size on 2D layout of MEDA based biochip, avoid droplet collision during routing and detect degraded electrodes, thus droplet detour possible. The architectural design improvement allows real time bioassay localized control of capacitive sensor, minimizes repetitive sensor actuation in energy energy-efficient manner. Such improvement and automatic sample dilution is not possible in DMFB architecture due to rigid fixed volumetric size of droplet uses for bioassay. Also minimization of waste generation and minimization of contamination of various samples is the key challenges in small chip area possesses some technical challenge need to be resolved.

The specific improvement areas related to an MEDA based biochip are identified as follows**:**

i. Dynamic real time droplet sensing: online real time checking of droplet position and maintenance of the desired concentration of samples is the most important concern and can be taken care of with newly AI-based algorithms for sample preparation.

ii. Cost-effective sample dilution strategy: efficient algorithm design for effective droplet routing and mixing to get the target concentration in time.

iii. Machine learning approach: Especially reinforcement learning based approach for the avoidance of droplet collision and detour in case of a degraded microelectrode for successful bioassay execution may be implemented.

iv. Avoidance of cross contamination: split less laminar mixing to minimize volumetric error to generate false positive results are the new research areas for further levels of innovation.

v. Energy efficient coordination: AI-based innovative design of microelectrodes on MEDA biochip can be targeted to consume less energy for repetitive actuations. This may be achieved using design optimization and algorithmic improvements on MEADA-based DMFB.

6. CONCLUSION

Sample preparation is an integral part of any bioassay execution. Considering sensitivity and specificity, various cost effective algorithmic dilution approaches are analyzed on MEDA architecture. We explored and compared waste efficient dilution on the MEDA-based point-of-care biochip.

Effective routing and design automation create dilution with target concentration factor through improved microelectrode architecture. Comparative analysis of automatic sample dilution and routing highlights MEDA based biochip gives better fluid management over traditional DMFB platform. In sample preparation through improvised reinforcement learning, thus avoiding droplet collision and degraded electrode sensing, can be implemented in the algorithmic level and Artificial Intelligence based approach can be adopted for automated sensing and fault recovery in the algorithm itself. There were limited research on cross contamination avoidance and scope for split less parallel multi target sample preparation. As a future research problem, it will be interesting to automatically prepare contamination-aware sample preparation, degraded microelectrode sensing and split-limited approach through advanced machine learning methods. AI-based automated sample preparation for MEDA biochips and self-correcting cyberphysical systems comprise of such chips can be targeted in the near future.

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