Digital microfluidic biochips (DMFBs) are revolutionizing many biochemical analysis procedures, e.g., high-throughput DNA sequencing and point-of-care clinical diagnosis. However, today’s DMFBs suffer from several limitations: (1) constraints on droplet size and the inability to vary droplet volume in a fine-grained manner; (2) the lack of integrated sensors for real-time detection; (3) the need for special fabrication processes and the associated reliability/yield concerns.

To overcome the above limitations, DMFBs based on a micro-electrode-dot-array (MEDA) architecture have recently been proposed. Unlike conventional digital microfluidics, where electrodes of equal size are arranged in a regular pattern, the MEDA architecture is based on the concept of a sea-of-micro-electrodes. The MEDA architecture allows micro-electrodes to be dynamically grouped to form a micro-component that can perform different microfluidic operations on the chip.

Design-automation tools can reduce the difficulty of MEDA biochip design and help to ensure that the manufactured biochips are versatile and reliable. In order to fully exploit MEDA-specific advantages (e.g., real-time droplet sensing), this dissertation research targets new design, optimization, and test problems for MEDA biochips.

II. HIGH-LEVEL SYNTHESIS FOR MEDA BIOCHIPS

High-level synthesis for DMFBs can be viewed as the problem of scheduling assay operations, binding operations to a given number of resources, configuring operations on the chip, and routing droplets to their destinations. The objective of high-level synthesis is to maximize parallelism, thereby decreasing completion time of bioassays.

In contrast to synthesis methods for conventional DMFBs, we proposed a unified synthesis flow that co-optimizes operation scheduling, module placement, and size-aware droplet routing for MEDA biochips [1], [2]; see Fig. 1. The priority controller dynamically generates priorities for the operations. The scheduler, placer, and router closely interplay with each other to determine the start/execution time for each operation, the location of each fluidic module, and droplet pathways between start locations and end locations.

Because the MEDA architecture can manipulate droplets of different sizes and droplets can move diagonally on the chip, we have developed an analytical model to determine the impact of droplet size and diagonal movement on droplet velocity. This model forms a key part of the routing component of the synthesis algorithm. We validated this model using a fabricated chip and showed that it correlates well with experimental results.

We also conducted experiments to validate the proposed synthesis technique. The proposed synthesis tool first generated the scheduling, module placement and droplet routing results for a given bioassay. Next, the experiment was carried out using a fabricated MEDA biochip and the control software. The close match between the simulation and experimental results shows that the simulated results can be used as an accurate predictor of results for an actual experimental setting.

III. ERROR RECOVERY IN MEDA BIOCHIPS

As in the case of integrated circuits, continued increase in the density and area of microfluidic biochips will also result in more defects and reduce yield. Fault models can be used to represent the effect of physical defects at some level of abstraction. These models can be used to capture the effect of defects that result in incorrect behavior.

In addition to defects and imperfections for fabricated MEDA-based biochips, faults may also arise during bioassay execution. Faults in biochips may eventually result in errors (e.g., a splitting operation with unbalanced droplets), which can adversely impact the correctness of the entire experiment. Therefore, efficient error-recovery strategies are required to ensure robust fluidic operations and high confidence in the outcome of biochemical experiments.

We have presented an error-recovery strategy to ensure the correctness of assays executed on MEDA biochips [3]. We first proposed a classification of the outcomes of operations into three categories: no error, minor error, and major error. Each outcome is treated in a different way in the proposed error-recovery strategy. By exploiting MEDA-specific advances in droplet sensing, we then presented a novel probabilistic timed automata (PTA)-based error-recovery technique to dynamically reconfigure the biochip using real-time data provided by on-chip sensors. An on-line synthesis
IV. SAMPLE PREPARATION ON MEDA BIOCHIPS

A potential important application of MEDA biochips lies in sample preparation via a series of dilution steps. The dilution of fluids plays a fundamental role in biomolecular protocols. Sample preparation is used to produce droplets with desired concentrations from stock solutions of reagents and samples. During sample preparation, reagent and sample droplets are repeatedly mixed with buffer droplets until the target concentration is obtained.

The main objective in sample preparation is to minimize: (1) the volume of sample needed (i.e., the number of sample droplets); (2) the amount of waste (i.e., the number of generated waste droplets); (3) the number of dilution operations, which determines the sample-preparation time.

We have presented a droplet size-aware and error-correcting sample-preparation method for MEDA biochips. In contrast to previous methods, the proposed approach considers droplet sizes and incorporates various mixing models in sample preparation. It utilizes MEDA-enabled microfluidic operations, and fully exploits the feature of real-time droplet sensing on MEDA biochips to correct errors during sample preparation.

As outlined in Fig. 3, there are three stages in the proposed sample-preparation algorithm: (1) dilution-graph (DG) generation, (2) droplet-cost table (DCT) construction, and (3) error-recovery graph (ERG) generation. First, the dilution graph is generated for the target droplet. Second, dilution graphs for all possible droplets are generated, and the corresponding generation costs are stored. Third, the error-recovery procedure is invoked if a concentration error is detected.

V. TEST METHODS FOR MEDA BIOCHIPS

In order to ensure an adequate quality level before their use for bioassay execution, MEDA biochips need to be screened for defects and incorrect fluidic operations. Therefore, effective test techniques are required before we can utilize high-level synthesis to map bioassay protocols to a MEDA biochip.

We have presented efficient test methods for MEDA biochips [4]. We first described various defects and malfunctions that are typical for MEDA biochips, and related these defects to fault models. We then proposed test techniques for structural test. A capacitive voltage divider is proposed and integrated into each microcell to facilitate the structural test. Finally, we developed cost-effective functional test techniques to test fundamental microfluidic operations on a target MEDA biochip. These techniques can identify “qualified regions” (i.e., groups of microelectrodes that pass functional test). We have evaluated the proposed test techniques using both simulation results as well as experimental results based on fabricated MEDA biochips.

VI. CONCLUSIONS

This dissertation research has presented a set of design automation techniques for MEDA biochips. In contrast to previous conceptual methods for conventional DMFBs, the proposed techniques address practical issues that arise in the design, utilization, and maintenance of MEDA biochips. By bridging the gap between theory and realistic applications on fabricated chips, these techniques provide efficient, powerful, and practical design-automation solutions for MEDA biochips. The list of publications related to this dissertation research is shown in [1]–[5].

REFERENCES


