Abstract

Recently, a new field of interdisciplinary research centered around "Lab-on-a-Chip (LoC)" has emerged which has wide applications to biochemistry and several healthcare domains such as for timely diagnosis of cardiovascular diseases, cancer, diabetes, and for mitigation of global HIV crisis. Typically, an LoC implements a biochemical laboratory test protocol (bioprotocol or bioassay) on a single chip that is a few square centimeters in size, which provides a low-cost and fast diagnostic solutions to a variety of medical applications. In particular, droplet-based microfluidic biochips have recently gained wide acceptance in developing LoC applications in contrast to continuous-flow microfluidic chips. The former class is commonly known as digital microfluidic (DMF) biochips. They use electrical actuation to manipulate (dispensing, transporting, merging, mixing, splitting) discrete droplets of nano- or pico-liter volume reactant (sample or reagent) fluids on a two-dimensional array of electrodes. A DMF biochip is dynamically reconfigurable and is capable of relocating microfluidic modules to other parts of the chip without affecting the functionality. Reconfiguration can be achieved by changing the electrode-actuation sequence, which is generated by a microcontroller attached to the system.

In almost all bioprotocols, dilution of a reactant fluid and mixture-preparation of several reactant fluids are two fundamental preprocessing steps. Since off-chip sample-preparation poses a significant hindrance to the overall bioassay completion time, for fast and high-throughput applications, sample preprocessing steps should also be automated on-chip, i.e., they need to be integrated and self-contained on the biochip itself. Until recently, only a few research articles have been reported for design automation of sample preparation of several reactant fluids using DMF biochips. In the $(1:1)$ mixing model, two equal-volume fluid droplets are mixed in one $(1:1)$ mixing step, followed by a balanced split, in which two droplets are produced. One mix, followed by a balanced split together, is called as a mix-split step. In this work, we propose several computer-aided-design (CAD) algorithms and techniques for the design-automation of on-chip sample-preparation of biochemical fluids using DMF biochips. Specifically, we have studied the following problems:

1. Dilution/Mixing of Biochemical Fluids with Reduced Wastage: In a bioassay, input sample and reagent biochemical fluids are very expensive and therefore, waste minimization is desirable while executing a bioassay with limited volume of expensive input fluids. Reducing the waste is also crucial for avoidance of cross-contamination and for reducing the overhead of waste droplet routing. This work proposes an optimization and automation technique for automated dilution/mixing that can significantly reduce the production of waste droplets compared to existing dilution algorithms. A layout is also proposed to implement the dilution algorithm to reduce the number of waste droplets.

2. Improved Dilution/Mixing of Biochemical Fluids and Integrated Dilution: For efficient on-chip dilution of a reactant fluid or mixing of two reactant fluids, it is desirable to reduce both the number of waste droplets and of the number of $(1:1)$ mix-split steps. In this work, we design an improved dilution algorithm that can further reduce the demand of input reactant fluids and production of

waste droplets with fewer (1 : 1) mix-split steps compared to earlier techniques. We also present an integrated scheme for diluting a fluid that allows us to choose the best algorithm for waste minimization among the three existing methods.

3. Dilution and Mixing from Arbitrary Concentrations of Biochemical Fluids: This work explores the problem of generalized dilution and mixing from a supply of two or more arbitrary concentrations of same/different reactant fluids (with a random value between the two boundaries of 100% and 0%).

4. Layout-Aware Mixture-Preparation of Three or More Biochemical Fluids: This work describes a layout-aware mixing algorithm and a routing-aware resource (fluid-reservoirs and on-chip mixers) allocation scheme for mixture-preparation for determining a suitable placement of boundary reservoirs and on-chip mixers on a DMF biochip.

5. Efficient Mixture-Preparation of Biochemical Fluids: In this work, we describe an efficient mixing algorithm that minimizes the wastage of reactant fluids and the number of (1 : 1) mix-split steps.

6. Demand-Driven Dilution and Droplet Streaming: In several situations, a dilution of a fluid may be required as multiple units. This work reports suitable scheduling schemes for generating multiple droplets of a given concentration factor with a minimum number of waste droplets and with the fewest mix-split steps.

7. Demand-Driven Mixture-Preparation and Droplet Streaming: In many real-life bioassays, a target mixture of several fluids may be needed repeatedly for successful assay completion. This work presents a droplet-streaming engine, which efficiently reuses the waste droplets from previous steps to reduce the wastage and the time of completion.

The thesis also presents extensive simulation results for validation of the proposed CAD algorithms.

Keywords: Digital Microfluidics, Biochips, Sample Preparation, CAD Algorithms, Optimization, Scheduling, Resource Allocation, Layout Design.