Design and Testing of Digital Microfluidic Biochips

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To my wife Xinying Li and to my parents Ning Zhao and Huaixiu Yan

By Yang Zhao

To my students over the years and to the tradition of excellence that they have established

By Krishnendu Chakrabarty

Preface

Digital microfluidics is an emerging technology that provides fluid-handling capability on a chip. Biochips based on digital microfluidics have therefore enabled the automation of laboratory procedures in biochemistry. By reducing the rate of sample and reagent consumption, digital microfluidic biochips allow continuous sampling and analysis for realtime biochemical analysis, with application to clinical diagnostics, immunoassays, and DNA sequencing. Recent advances in technology and applications serve as a powerful driver for research on computer-aided design (CAD) tools for biochips.

This book is focused on a design automation framework that addresses chip synthesis, droplet routing, control-pin mapping, testing and diagnosis, and error recovery. In contrast to prior work on automated design techniques for digital microfluidics, the emphasis here is on practical CAD optimization methods that can target different design problems in a unified manner. Constraints arising from the underlying technology and the application domain are directly incorporated in the optimization framework.

The avoidance of cross-contamination during droplet routing is a key design challenge for biochips. A droplet-routing method has been proposed to avoid cross-contamination in the optimization of droplet flow paths. The proposed approach targets disjoint droplet routes and synchronizes wash-droplet routing with functional droplet routing, in order to reduce the duration of droplet routing while avoiding the cross-contamination between different droplet routes. In order to avoid cross-contamination between successive routing steps, an optimization technique is used to minimize the number of wash operations that must be used between successive routing steps.

In pin-constrained digital microfluidic biochips, concurrently implemented fluidic operations may involve pin-actuation conflicts if they are not carefully synchronized. A two-phase optimization method has been proposed to identify and synchronize these fluidic operations. The goal is to implement these fluidic operations without pin-actuation conflict, and minimize the duration of implementing the outcome sequence after synchronization.

Due to the interdependence between droplet routing and pin-count reduction, this book presents two optimization methods to concurrently solve the droplet-routing and the pin-mapping design problems. First, an integer linear programming (ILP)-based optimization method has been developed to minimize the number of control pins. Next, an efficient heuristic approach has been developed to tackle the co-optimization problem.

Dependability is an important system attribute for microfluidic biochips. Robust testing methods are therefore needed to ensure correct results. This book presents a built-in self-test (BIST) method for digital microfluidic biochips. This method utilizes digital microfluidic logic gates to implement the BIST architecture. A cost-effective fault diagnosis method has also been proposed to locate a single defective cell, multiple rows/columns with defective cells, as well as an unknown number of rows/columns-under-test with defective cells. A BIST method for online testing of digital microfluidic biochips has been proposed. An automatic test pattern generation (ATPG) method has been proposed for non-regular digital microfluidic chips. A pin-count-aware online testing method has been developed for pin-constrained designs to support the execution of both fault testing and the target bioassay protocol.

To better monitor and manage the execution of bioassays, control flow has been incorporated in the design and optimization framework. A synthesis method has been developed to incorporate control paths and an error-recovery mechanism during chip design. This method addresses the problem of recovering from fluidic errors that occur during on-chip bioassay execution.

In summary, this book presents a set of unified design tools for digital microfluidics. This work is expected to reduce human effort during biochip design and biochip usage, and enable low-cost manufacture and more widespread adoption for laboratory procedures.

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