

Hardware/Software Co-Design and Optimization for Cyberphysical Integration in Digital Microfluidic Biochips

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*To my beloved grandfather and grandmother,
Junyi Luo and Fangzhen Wang — Yan Luo*

Preface

Microfluidic biochips have now come of age, with applications to biomolecular recognition for high-throughput DNA sequencing, immunoassays, and point-of-care clinical diagnostics. In particular, digital microfluidic biochips, which use electrowetting-on-dielectric to manipulate discrete droplets (or “packets of biochemical payload”) of picoliter volumes under clock control, are especially promising. The potential applications of biochips include real-time analysis for biochemical reagents, clinical diagnostics, flash chemistry, and on-chip DNA sequencing. The ease of reconfigurability and software-based control in digital microfluidics has motivated research on various aspects of automated chip design and optimization.

This book is focused on facilitating advances in on-chip bioassays, enhancing the automated use of digital microfluidic biochips, and developing an “intelligent” microfluidic system that has the capability of making on-line re-synthesis while a bioassay is being executed. This book includes the concept of a “cyberphysical microfluidic biochip” based on the digital microfluidics hardware platform and on-chip sensing technique. In such a biochip, the control software, on-chip sensing, and the microfluidic operations are tightly coupled. The status of the droplets is dynamically monitored by on-chip sensors. If an error is detected, the control software performs dynamic re-synthesis procedure and error recovery.

In order to minimize the size and cost of the system, a hardware-assisted error-recovery method, which relies on an error dictionary for rapid error recovery, is also presented. The error-recovery procedure is controlled by a finite-state machine implemented on a field-programmable gate array (FPGA) instead of as software running on a separate computer. Each state of the FSM represents a possible error that may occur on the biochip; for each of these errors, the corresponding sequence of error-recovery signals is stored inside the memory of the FPGA before the bioassay is conducted. When an error occurs, the FSM transitions from one state to another, and the corresponding control signals are updated. Therefore, by using inexpensive FPGA, a portable cyberphysical system can be implemented.

In addition to errors in fluid-handling operations, bioassay outcomes can also be erroneous due to the uncertainty in the completion time for fluidic operations. Due to the inherent randomness of biochemical reactions, the time required to complete each step of the bioassay is a random variable. To address this issue, a new “operation-interdependence-aware” synthesis algorithm is described in this book. The start and stop times of each operation are dynamically determined based on feedback from the on-chip sensors. Unlike previous synthesis algorithms that execute bioassays based on pre-determined start and end times of each operation, the proposed method facilitates “self-adaptive” bioassays on cyberphysical microfluidic biochips.

Another design problem addressed in this book is the development of a layout-design algorithm that can minimize the interference between devices on a biochip. A probabilistic model for the polymerase chain reaction (PCR) is described; based on the model, the control software can make on-line decisions regarding the number of thermal cycles that must be performed during PCR. Therefore, PCR can be controlled more precisely using cyberphysical integration.

To reduce the fabrication cost of biochips, yet maintain application flexibility, the concept of a “general-purpose pin-limited biochip” is presented. Using a graph model for pin-assignment, the book develops the theoretical basis and a heuristic algorithm to generate optimized pin-assignment configurations. The associated scheduling algorithm for on-chip biochemistry synthesis has also been developed. Based on the theoretical framework, a complete design flow for pin-limited cyberphysical microfluidic biochips is presented.

In summary, this book presents an algorithmic infrastructure as well as a set of optimization tools for cyberphysical system design and technology demonstrations. The results presented here are expected to enable the hardware/software co-design of a new class of digital microfluidic biochips with tight coupling between microfluidics, sensors, and control software.

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