Special Session

Continuous-Flow Biochips: Current Platforms and Emerging Research Challenges

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Motivation for Special Session:

Microfluidic biochips are replacing the conventional biochemical analyzers, by integrating all the necessary functions for biochemical analysis using microfluidics. The trend today is towards microfluidic platforms, which provide "a set of fluidic unit operations, which are designed for easy combination within a well- defined fabrication technology", and offer a "generic and consistent way for miniaturization, integration, customization and parallelization of (bio-)chemical processes". Microfluidic platforms are used in many application areas, such as, in vitro diagnostics (point-of-care, self-testing), drug discovery (high-throughput screening, hit characterization), biotech (process monitoring, process development), ecology (agriculture, environment, homeland security). There are two main technologies for implementing microfluidic biochips: (1) continuous-flow, based on the manipulation of continuous liquid through fabricated micro-channels, using external pressure sources or integrated mechanical micro-pumps, and (2) droplet-based, in which the liquid is manipulated as discrete droplets on a two dimensional array of identical electrodes. The focus of this special session is on (1) continuous-flow biochips, where the basic building block is a valve, which can be fabricated at very high densities, e.g., 1 million valves per cm2. By combining these valves, more complex units such as mixers, switches, multiplexers can be built up and the technology is therefore referred to as microfluidic Very Large Scale Integration (mVLSI).

To realize such biochips, the integration of embedded systems and microfluidics inevitably leads to a new research dimension for More than Moore and beyond. The manufacturing technology for the mVLSI biochips has advanced faster than Moore's law, and there are currently several companies that offer complete programmable biochip solutions (e.g., Microfluidic Innovations, Inc.) and fabrication foundries that can fabricate a biochip from a layout in AutoCAD (e.g., The Kavli Nanoscience Institute Microfluidic Foundry at Caltech). However, the design methodologies are still manual and bottom-up. Designers use drawing tools, e.g., AutoCAD, to manually design the chip. In order to run the experiments, applications are manually mapped onto the valves of the chips (analogous to exposure of gate-level details in electronic integrated circuits). Since mVLSI chips can easily have thousands of valves, the manual process can be very time-consuming, error-prone and result in inefficient designs and mappings. Recent research has addressed these challenges, and, inspired by the methods and tools taken for granted in the EDA community, has started to propose approaches for the top-down design automation of continuous-flow biochips. For example, languages such as BioCoder and Aqua have been proposed to capture biochemical applications. In addition, initial proof-of-concept algorithms have been adapted from EDA for the physical design (e.g., placement, routing) and application mapping (e.g., binding, scheduling) as well as testing and reliability optimization. This is a novel and multidisciplinary topic, not covered in the regular sessions of the conference, but of relevance to the VLSI Design community. This special session will introduce attendees to the recent platforms and emerging research challenges in the area of continuous-flow microfluidics. We believe that the special session

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will generate interest in this topic, leading to more research, aiming at delivering complete EDA tool-flows for this emerging area.

Organizers' Biographies

Paul Pop is an Associate Professor at DTU Compute, Technical University of Denmark (DTU). He has received his Ph.D. degree in computer systems from Linköping University in 2003. His main research interests are in the area of system-level design of embedded systems. He has published extensively in this area, and has received the best paper award at the DATE 2005, RTiS 2007, CASES 2009 and MECO 2013. He has also received the EDAA Outstanding Dissertations Award (co-supervisor) in 2011 and DTU's prize for "Research-based public-sector consultancy" in 2013. He has served on the technical program committee of numerous conferences, such as DATE, ICCAD, CODES+ISSS, EMSOFT, ASP DAC, RTCSA and RTSS, and is a frequent reviewer for the top journals in the area. He is the Chairman of the IEEE Danish Chapter on Embedded Systems, Coordinator of the Danish national InfinIT Systems Engineering Interest Group and a founding member of the Danish Chapter of INCOSE. Since 2007 he is the coordinator of a research group focusing on CAD for biochips, composed of two senior researchers, three PhD students and several master students. His work on design techniques for biochips has received the best paper award at the CASES 2009 conference. He has co-organized and participated in tutorials and special sessions on CAD for biochips at conferences such as SOCC 2011 and ESWEEK 2011.

Tsung-Yi Ho received his Ph.D. degrees in Electrical Engineering from National Taiwan University, Taipei, Taiwan, ROC, in 2005. He is a Professor with the Department of Computer Science of National Chiao Tung University, Hsinchu, Taiwan. From 2007 to 2014, he was with National Cheng Kung University, Tainan, Taiwan. His research interests include design automation for microfluidic biochips and nanometer integrated circuits. He has published several papers in top journals and conferences such as IEEE TCAD, ACM TODAES, ACM/IEEE DAC, IEEE/ACM ICCAD, ACM ISPD, and etc. He presented 8 tutorials and contributed 4 special sessions in ACM/IEEE conferences, all in design automations on biochips. He was the recipient of many research awards, such as Dr. Wu Ta-You Memorial Award of National Science Council (NSC) of Taiwan (the most prestigious award from NSC for junior researchers), Distinguished Young Scholar Award of Taiwan IC Design Society, Outstanding Young Electrical Engineer Award of Chinese Institute of Electrical Engineering, K. T. Li Research Award of Delta Electronics, ACM Taipei Chapter Young Researcher Award, IEEE Tainan Chapter Gold Member Award, the Invitational Fellowship of the Japan Society for the Promotion of Science (JSPS), Japan, and the Humboldt Research Fellowship from the Alexander von Humboldt Foundation, Germany. Currently, he serves as a Distinguished Visitor of the IEEE Computer Society, the Chair of IEEE Computer Society Tainan Chapter, and an Associate Editor of *ACM Journal on Emerging Technologies in Computing Systems* and *IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems*. He is a senior member of IEEE.

Krishnendu Chakrabarty received the B. Tech. degree from the Indian Institute of Technology, Kharagpur, in 1990, and the M.S.E. and Ph.D. degrees from the University of Michigan, Ann Arbor, in 1992 and 1995, respectively. He is now the William H. Younger Distinguished Professor of Engineering in the Department of Electrical and Computer Engineering at Duke University. He is also the Executive Director of Graduate Studies in Electrical and Computer Engineering and a Professor of Computer Science at Duke University. He is also a Chair Professor in Software Theory at Tsinghua University, Beijing, China, and a Visiting Chair Professor at the National Cheng Kung University in Taiwan. Prof. Chakrabarty is a recipient of the National Science Foundation Early Faculty (CAREER) award, the Office of Naval Research Young Investigator award, and the Humboldt Research Award from the Alexander von Humboldt Foundation, Germany, and 10 papers awards at major IEEE conferences. He was a Mercator Visiting Professor of Deutsche Forschungsgemeinschaft at University of Potsdam, Germany during 2000-2002.

Prof. Chakrabarty's current research projects include: testing and design-for-testability of SOCs and 3D ICs; microfluidics, biochips and cyberphysical systems; optimization of digital print and production system infrastructure.

He has authored 15 books on these topics (with two more books in press), 24 invited book chapters, published over 480 papers in journals and refereed conference proceedings, and given over 210 invited, keynote, and plenary talks. He has also delivered over 30 tutorials at leading conferences, including numerous tutorials on microfluidic biochips. He has an h-index of 59 and his work has received nearly 15,600 citations. In the Microsoft Academic Search website (as of May 29, 2014), Prof. Chakrabarty's in-domain citation count for the last 10 years ("Top Authors in Hardware and Architecture") is ranked no. 9 among 20,000 researchers worldwide.

Prof. Chakrabarty is a Fellow of ACM, a Fellow of IEEE, aand Golden Core Member of the IEEE Computer Society. He was a 2009 Invitational Fellow of the Japan Society for the Promotion of Science (JSPS). He is a recipient of the 2008 Duke University Graduate School Dean's Award for excellence in mentoring, and the 2010 Capers and Marion McDonald Award for Excellence in Mentoring and Advising, Pratt School of Engineering, Duke University. He served as a Distinguished Visitor of the IEEE Computer Society during 2005-2007 and 2010 2012, and as a Distinguished Lecturer of the IEEE Circuits and Systems Society during 2006-2007 and 2012-2013. Currently he serves as an ACM Distinguished Speaker. He served as the Editor-in-Chief of *IEEE Design & Test of Computers* during 2010-2012. Currently he serves as Editor-in-Chief of *ACM Journal on Emerging Technologies in Computing Systems*. Prof. Chakrabarty is also an Associate Editor of *IEEE Transactions on Computers and IEEE Transactions on Biomedical Circuits and Systems*. In the recent past, he has served Associate Editor of *Computer*3 *Aided Design of Integrated Circuits and Systems*, *IEEE Transactions on Circuits and Systems I, IEEE Transactions on Circuits and Systems II*. He serves as an Editor of the *Journal of Electronic Testing: Theory and Applications* (JETTA), and on the steering committee of *IEEE Transactions on VLSI Systems* and *IEEE Journal on Exploratory Solid-State Computational Devices and Circuits*.

William Grover is an Assistant Professor in the Department of Bioengineering in the Bourns College of Engineering at the University of California, Riverside. At UC Riverside, Dr. Grover's lab develops microfluidic instruments for analyzing the fundamental physical properties (mass, volume, density, etc.) of single living cells and microorganisms. Prior to joining UC Riverside, Dr. Grover received his postdoctoral training in the Biological Engineering Division at Massachusetts Institute of Technology. At MIT, Dr. Grover developed a microfluidic technique for making the first precision measurements of the density of single living cells. Dr. Grover obtained his Ph.D. in Chemistry at the University of California, Berkeley. At UC Berkeley, Dr. Grover developed the first microfluidic valves suitable for large-scale use in glass microfluidic devices. Now cited over 400 times and the subject of several issued US patents, this valving technology is the technological foundation of one company (IntegenX, Pleasanton, CA) and several academic research labs.

Contributed Presentations in the Special Session

Designing, Fabricating, and Using Flow-Based Microfluidics: Past Successes and Future Challenges
William H. Grover

Abstract: The field of microfluidics—the manipulation of fluids on the micron scale—is now 35 years old. Like many people entering middle age, microfluidics is at the threshold between a successful past and an uncertain future. Fabrication techniques adapted from the semiconductor industry have enabled us to build incredibly complex fluidic chips that help us diagnose diseases, understand how our bodies function, and monitor the environment. However, the off-chip hardware that supports the function of these chips has remained virtually unimproved for decades, and the process used to design new microfluidic chips remains extremely laborintensive. These deficiencies dramatically slow the development of new microfluidic chips and make existing microfluidic instruments too large, too expensive, and too power-hungry for life-saving use in many resourcelimited or point-of-care settings. In this talk, we will survey the existing techniques for designing, manufacturing, and using flow-based microfluidic devices. We will focus on the strengths and deficiencies of these existing methods, drawing extensively on the speaker's 15 year history in the development and commercialization of microfluidic instruments. Particular

attention will be paid to microfabricated valves and pumps: how they work to control fluid, how they are fabricated, what are their disadvantages, and how to reduce or eliminate these disadvantages by using principles from computer science and electrical engineering.

Design Automation for Flow-Based Biochips: System-Level Modeling, Techniques, and Experimental Validation

Paul Pop

***Abstract**:* Flow-based microfluidic biochips are presently designed and laid out by hand using software such as AutoCAD. These design methodologies are akin to transistor-level design of semiconductor circuits, which has since been supplanted by VLSI design automation. In order to raise the level of abstraction of biochip design, specification, and validation, comparable design automation technologies are necessary. The first part of this talk will focus on recent advances in physical design automation (placement and routing) for the flow and control layers of flow-based microfluidic biochips. Considering that the architecture of the biochip is given, the second part of that talk will discuss techniques for the binding of operations in the application to the functional units of the architecture, the scheduling of operations and the routing and scheduling of the fluid flows, such that the application completion time is minimized. We will cover a topology graph-based model for the biochip architecture, and a sequencing graph to model for biochemical application, showing how the application model can be obtained from biochemical programming languages such as BioCoder and Aqua. We present a List Scheduling-based Application Mapping framework and evaluate it by using real-life as well as synthetic benchmarks. We also discuss the validation of the results on a biochip platform from Microfluidics Innovation, Inc.

Testing of Flow-Based Microfluidic Biochips: Fault Modeling, Design-for-Testability, and Experimental Demonstration

Krishnendu Chakrabarty

***Abstract**:* Recent advances in flow-based microfluidics have led to the emergence of biochemistry-on-a-chip as a new paradigm in clinical diagnostics and biomolecular recognition. However, a potential roadblock in the deployment of microfluidic biochips is the lack of test techniques to screen defective devices before they are used for biochemical analysis. Defective chips lead to repetition of experiments, which is undesirable due to high reagent cost and limited availability of samples. Prior work on fault detection in biochips has been limited to digital ("droplet") microfluidics and other electrode-based technology platforms. This talk will present the first approach for automated testing of flow-based microfluidic biochips that are designed using membrane-based valves for flow control. The proposed test technique is based on a behavioral abstraction of physical defects in microchannels and valves. The flow paths and flow control in the microfluidic device are modeled as a logic circuit composed of Boolean gates, which allows test generation to be carried out using standard Automatic Test Pattern Generation (ATPG) tools. The tests derived using the logic circuit model are then mapped to fluidic operations involving pumps and pressure sensors in the biochip. Feedback from pressure sensors can be compared to expected responses based on the logic circuit model, whereby the types and positions of defects are identified. We show how a fabricated biochip can be tested using the proposed method, and demonstrate experimental results for two additional fabricated chips.