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Microfluidic Biochips: Bridging Biochemistry with Computer Science and Engineering

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February 27–March 2, 2017

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Microfluidic Biochips: Bridging Biochemistry with Computer Science and Engineering

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Advances in microfluidic technologies have led to the emergence of biochip devices for automating laboratory procedures in biochemistry and molecular biology. These devices enable the precise control of nanoliter-scale biochemical samples and reagents. Therefore, Integrated Circuit (IC) technology can be used to transport a "chemical payload" in the form of micro- or nano-fluidic carriers such as droplets or as bulk flow in microchannels. As a result, non-traditional biomedical applications and markets (e.g., high-throughput DNA sequencing, portable and point-of-care clinical diagnostics, protein crystallization for drug discovery) are opening up for ICs and systems. This represents a More than Moore-approach.

However, continued growth (and larger revenues resulting from technology adoption by pharmaceutical and healthcare companies) depends on advances in chip integration and design-automation tools. Thus, there is a need to deliver the same level of Computer-Aided Design (CAD) support to the biochip designer that the semiconductor industry now takes for granted. In particular, these CAD tools will adopt computational intelligence for the optimization of biochip designs. Also, the design of efficient CAD algorithms for implementing biochemistry protocols to ensure that biochips are as versatile as the macro-labs that they are intended to replace. This is therefore an opportune time for the software and semiconductor industry as well as circuit/system designers to make an impact in this emerging field.

Recent years have therefore seen growing interest in design methods and design-automation tools for the digital microfluidic platform with special issues of IEEE Transactions on CAD and IEEE Design & Test of Computers, special sessions at DAC, ISPD, ASPDAC, and ICCAD, as well as workshops/tutorials at ISCAS, ICCAD, SOCC, and DATE. A number of CAD research groups worldwide (US, Germany, Taiwan, Denmark, China, Japan, India, etc.) have initiated research projects on CAD for microfluidic biochips.

The goal of the meeting is to bring together experts in order to present and to develop new ideas and concepts for the design automation algorithms and tools for microfluidic biochips. This meeting also provides a unique opportunity to bring chip designers, bioengineers, biochemists, and theoretical computer sci-

entists together for comprehensive discussions on the research tasks as well as commercial prospects in this domain. Areas ranging from architecture, synthesis, optimization, verification, testing, and beyond should be covered. Topics to be discussed include but are not limited to the following:

- Architectural synthesis
- Behavior-level synthesis
- Cooling for integrated circuits
- Cross-contamination removal
- Cyberphysical integration
- Device modeling
- Drug-delivery biochips
- Fault modeling, testing, and protocol verification
- Light-actuated biochips
- Numerical simulation
- On-chip sensors
- Paper-based microfluidics
- Particle microfluidics
- Physical design
- Pin-constrained design
- Sample preparation

As possible results, we expect to see a better understanding of the respective areas, new impulses for further research directions, and ideas for areas that will heavily influence research in the domain of design automation on microfluidic biochips within the next years. The meeting will facilitate greater interdisciplinary interactions between researchers in chip designers, bioengineers, biochemists, and theoretical computer scientists.

Meeting Schedule

Monday, February 27, 2017: Tutorials & Talks

- Introduction of the participants
- Paper-based Digital Microfluidic Biochips
  - Kwanwoo Shin: Overview on Paper-based Digital Microfluidic Biochips
  - Jan Madsen: DTU's vision on paper-based DMFs
  - Hailong Yao: Control-fluidic CoDesign for paper-based digital microfluidic biochips
- Networked Labs-on-Chip
  - Robert Wille: The Concept of NLoCs: Introducing a Biocompatible LoC Technology
  - Werner Haselmayr: Building Proper NLoCs: Realizing the Droplet Flow in NLoCs
  - Andreas Grimmer: Towards Push-button Solutions: Design Automation for NLoCs
- Digital Microfluidic Biochips/Electrowetting-based Biochips
  - Oliver Keszocze: Different Cell-Shapes and Sea-of-micro-electrodes: Recent Advances in the Design of Electrowetting-based Biochips
  - Sudip Roy: Design Automation Issues for On-Chip Mixture Preparation using Digital Microfluidic Biochips
- Flow-based Biochips
  - Ulf Schlichtmann, Bing Li: Architectural Synthesis of Flow-based Biochips
- Reports, Insights, and (provacative) Views
  - Krishnendu Chakrabarty: Why current design automation research is absolutely useless in practice and how can we make our work relevant for microbiology

Tuesday, February 28, 2017: Follow Ups, Working Groups, and Excursion

- Talks
  - Thomas Chen: Applications of Microfluidic Devices in Sensor Systems
  - Hao Yu: CMOS Integrated Lab-on-a-chip System for Personalized DNA Sequencing
- Follow Up: Networked Labs-on-Chip

- Follow Up: Benchmarks and Realistic Application
  - Collecting and sharing benchmarks
  - Possible formats (Aqua, Blockly, ...)
  - How to get "end users" involved?
  - How does it fit into our current publishing activities?
- Excursion

Wednesday, March 1, 2017: Demos, Hands-on Experiences, Discussions, etc.

- Demos, Hands-on Experiences
  - Print & Go: Physical Realization of Networked Labs-on-Chip
  - Digital Microfluidic Biochips
  - Paper-based Digital Microfluidics
  - Biochips for personal use: how usable is our system for non-experts?
- Talk
  - Shih-Kang Scott Fan: Constructing 3D Heterogeneous Hydrogels on an Electromicrofluidic Platform

Thursday, March 2, 2017: Consolidation and Plans for the Future

Overview of Talks and Position Statements

Paper Based DMF Chips for lab automation

Kwanwoo Shin (Sogang University Seoul, Korea)

Recently, we have presented a novel paper-based fluidic chip that can enable the full range of fluidic operations by implementing an electric input on paper via an electrowetting technique. This powered paper-based microfluidic chip, which is known as an *active paper open chip* (APOC), is primarily characterized by discrete drop volumes and is an open-type chip. These active, paper-based, microfluidic chips driven by electrowetting are fabricated using inkjet printing technique and demonstrated for discrete reagent transport and mixing. Instead of using the passive capillary force on the pulp in the paper to actuate a continuous flow of a liquid sample, a single, discrete drop or a group of digital liquid drops are perfectly transported along programmed trajectories. The patterned electrodes, which are designed on a desktop computer, are printed on low-cost paper, such as recycled magazine papers, with conductive CNT ink using an office inkjet printer, which should enable true point-of-care production and diagnostic activities. We will present our newly developed active paper open chips, fabricated by an inkjet printing, and their lab automation application, which can readily accomplished, simplifying the workflow and improving the reaction accuracy tremendously in the laboratory to the conventional methods, often requiring multiple pre-treatments, mixing, separation, and thermal treatment on a single paper chip design. We will outline how this chip design can be fabricated, and present the extensive hands-on experiments to audience.

Control-Fluidic CoDesign for Paper-Based Digital Microfluidic Biochips

Hailong Yao (Tsinghua University, China)

Paper-based digital microfluidic biochips (P-DMFBs) have recently emerged as a promising low-cost and fast-responsive platform for biochemical assays. In P-DMFBs, electrodes and control lines are printed on a piece of photo paper using inkjet printer and conductive ink of carbon nanotubes (CNTs). Compared with traditional digital microfluidic biochips (DMFBs), P-DMFBs enjoy notable advantages, such as faster in-place fabrication with printer and ink, lower costs, better disposability, etc. Because electrodes and CNT control lines are printed on the same side of a paper, a new design challenge for P-DMFB is to prevent the interference between moving droplets and the voltages on CNT control lines. These interactions may result in unexpected droplet movements and thus incorrect assay outputs.

To address the new challenges in automated design of P-DMFBs, this paper proposes the first control-fluidic codesign flow, which simultaneously adjusts the control line routing and fluidic droplet scheduling to achieve an optimized solution. As the control line routing may not be able to address all the interferences between moving droplets and the voltages on control lines, droplet re-scheduling is performed to effectively deal with the remaining interferences in the routing solution. Computational simulation results on real-life bioassays

show that the proposed codesign method successfully eliminates all the interferences, while a state-of-the-art maze routing method cannot solve any of the benchmarks without conflicts.

The Concept of NLoCs: Introducing a Biocompatible LoC Technology

Robert Wille (Johannes Kepler University Linz, Austria)

In this talk, we introduced an emerging and biocompatible microfluidic technology called *Networked Labs-on-Chip* (NLoC). In NLoCs, tiny volumes of fluids, so-called droplets, flow in a continuous phase inside channels of micrometer-size (triggered by pressure). The closed channels allow for an incubation and storage of liquid assays over a long period of time and, by this, avoid evaporation and unwanted reactions. Recently, networking functionalities have been proposed, which enable the designer to dynamically select the operations to be conducted. These networking functionalities exploit hydrodynamic forces acting on droplets, and hence, increase the flexibility, effectiveness, as well as re-usability of NLoCs. Besides that, NLoC devices can be produced at low cost (e.g. using 3D printers) and are easy to use.

Experiments are conducted by executing operations on the droplets. These operations are implemented by modules, which are arranged along multiple paths through the NLoC. The paths are built by bifurcations of channels, i.e. the splitting of a channel in two or more successor channels. These successor channels of a bifurcation have different fluidic resistances which are mainly defined by their geometries, e.g. the longer the channel the higher the resistance and the smaller the section the higher the resistance. When a single droplet arrives at a bifurcation, it flows into the channel with the lower resistance. By that, the droplet itself increases the channels hydraulic resistance and, therefore, temporarily "blocks" this channel for following droplets. This principle of selectively blocking channels is eventually used to route droplets through the NLoC.

Building Proper NLoCs: Realizing the Droplet Flow in NLoCs

Werner Haselmayr (Johannes Kepler University Linz, Austria)

This talk covered the realization of the droplet flow in NLoCs devices. Technically, the movement of droplets depends on the applied pump, which produces a flow of a continuous phase, as well as the channels and modules which change the distribution of that flow depending on their resistances and their arrangement. More precisely, the resulting flow distribution in the NLoC can be described with the following parameters: (1) Each channel/module poses a fluidic resistance R for the flow, (2) the volume of the continuous fluid Q through the channel/module per time unit is called volumetric flow rate, and (3) the difference of the pressure ΔP of the volume at the input and the outlet of the channel/module is called pressure gradient. The Hagen-Poiseuille equation describes the relation between these parameters by $\Delta P = RQ$. This is similar to the well-known Ohm's law $V = RI$ from electronics, where the fluidic

resistance, the volumetric flow, and the pressure gradient are counterparts of the resistance R of a resistor, the current I, and the voltage V, respectively. In fact, the interplay between these flow parameters can directly be represented by the Ohm's law and, hence, the rules from electronics (e.g. Kirchhoffs Laws) can also be employed for NLoCs.

Towards Push-button Solutions: Design Automation for NLoCs

Andreas Grimmer (Johannes Kepler University Linz, Austria)

Finally, challenges on the design of NLoC devices are addressed. Due to the physical constraints and further interdependencies, the design of corresponding devices is a complex task. Thus far, only very prototypical and highly restricted NLoC devices have been fabricated and their designs almost entirely rely on manual labor. We aim for providing a tool support for important design steps including (1) determining an optimized NLoC architecture for a given set of experiments, (2) mapping the resulting architecture to a physical blueprint, and, finally, (3) determining droplet sequences eventually realizing the desired experiments. Overall, our methods will provide substantial contributions to the physical realization of corresponding devices and, for the first time, will allow users to easily and automatically design their experiments.

Different Cell Shapes and Sea-of-Micro-Electrodes: Recent Advances in the Design of Electrowetting-based Biochips

Oliver Keszocze (University of Bremen, Germany)

Recent advances in the underlying technology of electrowetting-based biochips allowed for a new type of biochip: sea-of-micro-electrodes biochips (also called micro-electrode-dot-array, or MEDA, biochips for short). While different shapes of cells (besides the commonly used squares also triangles and hexagons) have been reported earlier, MEDA chips allow for different shapes of droplets, as the on to one correspondence between cell and droplet is removed. In fact, droplets cover multiple cells at once. In the talk, different cell shapes as well as MEDA biochips have been introduced and corresponding discrete models were presented. These models were used 1) to prove that the complexity of finding routes of given lengths is NP-complete 2) as input for an automated reasoning engine producing exact, that is, minimal routing results. These exact results allow, besides determining routes for nets, for investigating properties of the lengths of the routes on the different biochips (different shapes or MEDA). More precisely, the question which cell shapes results in the shortest routes on "conventional" biochips or whether droplet shape changing instead of diagonal movement on MEDA biochips has the biggest impact on the routes can be answered.

Architectural Synthesis of Flow-based Microfluidic Biochips

Ulf Schlichtmann, Bing Li (Technical University of Munich, Germany)

Flow-based microfluidic biochips have attracted much attention in the EDA

community due to their miniaturized size and execution efficiency. Previous research, however, still follows the traditional computing model with a dedicated storage unit, which actually becomes a performance bottleneck of biochips.

In this talk, we investigate the fluid transportation and storage problem and describe an architectural synthesis framework considering distributed storage, which is constructed temporarily from transportation channels to cache fluid samples. Since distributed storage can be accessed more efficiently than a dedicated storage unit and channels can switch between the roles of transportation and storage easily, biochips with this distributed computing architecture can achieve a higher execution efficiency even with fewer resources.

At the end of the talk, we also raise the question about the trend of the research on microfluidic biochips. With different manufacturing technologies, biochips have diversified into subcategories such as digital biochips, flow-based biochips and networked labs-on-chip. Whether researchers in this community should focus on a unified development model/interface, or they should focus on each technology individually, has been discussed in the following session.

Why Current Design Automation Research is Absolutely Useless in Practice and How Can We Make Our Work Relevant for Microbiology?

Krishnendu Chakrabarty (Duke University, USA)

Microfluidics technology has shown considerable promise for advancing sample preparation and point-of-care diagnostics. Microfluidics provides rapid sample processing and the precise control of small volumes of liquid; therefore, it has the potential to transform microbiology and biochemistry research. Over the past decade, a number of microfluidics design-automation ("synthesis") techniques have been developed for on-chip fluidic manipulation. However, these methods overlook the myriad complexities of biomolecular protocols and they have yet to make an impact in biochemistry/microbiology research. There is very little concrete evidence of the adoption of digital microfluidics in mainstream microbiology research. My premise is that current synthesis techniques will never be able to cross the formidable barrier that separates engineering (or chip design) from practical microbiology. A paradigm shift in biochip design automation and a "phase transition" in research are clearly needed to bridge this gap between microfluidics and microbiology.

In this presentation, I explained how researchers from design-automation and embedded systems can play a key role in this transition. I presented a new synthesis flow that uses realistic models of biomolecular protocols and cyberphysical adaptation to address real-world microbiology applications. The presentation was centered on realistic case studies involving quantitative gene expression analysis and epigenetics. I presented a proposal on a standardized list of metrics that can be used for the assessment of design-automation techniques. A presentation of this type will serve as a "call to arms" for more focused and relevant research to increase the adoption of digital microfluidics in translational research for point-of-care diagnostics, as well as for the detection and treatment of diseases such as cancer.

Applications of Microfluidic Devices in Sensor Systems

Thomas Chen (Colorado State University, USA)

This talk focuses on two main applications of microfluidic devices: the integration of microfluidic devices with high-density microelectrode arrays for better understanding cellular communication in biological systems, and the integration of microfluidic devices with multiplexed affinity sensors for pathogen detection. Results from research at Colorado State University in these two areas have demonstrated the importance of enabling highly sensitive biological sensor systems by microfluidic devices. This talk also speculates potential applications of the digital microfluidics technology for future integrated biological sensor systems.

CMOS Integrated Lab-on-a-chip System for Personalized DNA Sequencing

Hao Yu (Nanyang Technological University, Singapore)

Considering the current aging society, the future personalized diagnosis requires portable biomedical devices with miniaturization of bio-instruments. The recent development of lab-on-a-chip (LoC) technology has provided a promising integration platform of CMOS integrated sensor, microfluidic channel, and MEMS. This talk will report the recent progress in CMOS integrated LoC system for personalized DNA sequencing at academia and also industry, including the recent works at NTU CMOS Emerging Technology Group (http://www.ntucmosetgp.net/). Traditional CMOS ion-sensitive-field-effect-transistor (ISFET) has poor pH detection sensitivity as well as faulty pH values. The first selected work is about a dual-mode (chemical + optical) CMOS ISFET sensor, which can improve sequencing accuracy significantly by correlated readout of chemical pH value at location-determined microbead via optical contact imaging. The second selected work will further discuss a high-sensitivity subthreshold readout of pH value by current-to-time-to-voltage conversion (C-TVC), which can reach ¡1mV or 1pA resolution with fast detection time. By utilizing C-TVC readout scheme, it is possible to identify single nucleotide bases required in the 4th generation DNA sequencing system (Nanopore) with CMOS-compatible solid-state pore (Si3N4/SiO2 membrane).

List of Participants

- ShihKan (Fan National Taiwan University, Taiwan)
- Ulf Schlichtmann (Technical University at Munich, Germany)
- Kwanwoo Shin (Sogang University, Korea)
- Hailong Yao (Tsinghua University, China)
- Hao Yu (Nanyang Technological University, Singapore)
- Bing Li (Technical University at Munich, Germany)
- Jan Madsen (Technical University of Denmark, Denmark)
- Oliver Keszocze (DFKI, Germany)
- Sudip Roy Indian (Institute of Technology at Roorkey, India)
- Andreas Grimmer (Johannes Kepler University, Linz Austria)
- Werner Haselmayr (Johannes Kepler University, Linz Austria)
- Mirela Alistar (Hasso-Plattner-Institut, Germany)
- Thomas W. Chen (Colorado State University, USA)
- Veasna Soum (Sogang University, Cambodia)
- Haena Cheong (Sogang University, Korea)